THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

VOL. 63 FEBRUARY, 1950 No. 2

THE DIFFERENTIATION OF CELLS AND TISSUES

CALDWELL LECTURE, 1949*

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FIRST, I express appreciation for the honor you have given me and for the opportunity to discuss with you, in this Caldwell Lecture, questions which have interested very many people, including the staffs of our Institutes, for many years.

This business of the differentiation of cells and their concomitant and subsequent organization into tissues, parts, and organs, is the very essence of a large part of biology and medicine. Applications ramify into every nook and corner of our daily thinking and work. These processes made us and our patients what we are; in fact, make all living things what they are.

In the beginning nothing was known of the effects of roentgen rays on living cells, but it was soon manifested that roentgen rays destroyed cells. It took a longer time to add to this finding the significant one that cells exposed to irradiation but not destroyed could, in their subsequent life cycle, produce undesirable and even have fatal end-results. Radiologists now are in a better position, since so many of the effects of radiations have been described and cataloged. For example, their power to produce mutation and chromosome breakage has been known since 1927. But no end of problems remain confronting the radiologist. The changes in cells and their destruction caused by irradiation remain to be understood in terms of fundamental biological concepts. Are all of the changes to be understood as alterations in chromosomes, or must the search be carried further to understand why some tissues are resistant and others susceptible? For example, it is a common experience that poorly differentiated tissue in general is more susceptible to irradiation than is more highly differentiated tissue. The key question, from this point of view, is the nature of differentiation. What are the changes that cause cells to be different from each other, and what is the nature of the difference? What factors cause differentiation to begin in cells? What are the relative roles of the nucleus and cytoplasm during differentiation? These and many other questions fundamental to radiological practice, as well as many other fields, therefore determine that my talk will be largely concerned with an analysis of differentiation.

Years ago, William Harvey headed one of the chapters in his book, "Exercitationes Generatione Animalium," with the whimsical title, "The Efficient Cause of the

* Delivered at the Fiftieth Annual Meeting of the American Roentgen Ray Society, Cincinnati, Ohio, October 4–7, 1949.

Chicken is Hard To Be Found Out." It certainly is, for we are still working on it centuries later; rather we know it is probably even more difficult than Harvey suspected, though we cannot really know that. But why the "Efficient Cause"? The expression is a philosophical one, and has changed from age to age. It dates from Aristotle, as rephrased by George Santayana, who lists Aristotle's four causes as:

The Material Causes; e.g., an egg, not a stone
The Efficient Causes; i.e., warmth of the hen
The Formal Causes; i.e., a particular egg (chicken, sea urchin, human)
The Final Causes; i.e., an ideal egg.

Of these four causes, present-day science recognizes only two—the material and the efficient, and in quite a different form. Each generation has striven for explanations of "Efficient Causes"—Harvey's being different from Aristotle's. Some of our workers today, still striving for efficient causes, have evolved concepts different from those held by Harvey or Aristotle and many others through the ages. We generalize—and by preference we use detailed chemical and physical approaches wherever possible.

But the semi-mystical approach survives even to the present time, in what is called Psychobiology or Hormism. Samuel Butler, a strong exponent of this viewpoint, conceived of our subject—differentiation—thus: "I want to connect the actual manufacture of the *things* a chicken makes inside an egg with a *desire* and *memory* of the chicken, so as to show that one and the same set of *vibrations* at once change the universal substratum into the particular phase of it required, and awaken a *consciousness of* and a *memory of* and a *desire toward* this particular phase on the part of the molecules which are being vibrated into it." Mystical and metaphysical it is true, and condemned as barren toward understanding and progress, but—let us see what a distinguished professor of chemistry (Andrews) has said recently—"Through the atom (science) is giving us an insight into the nature of the world in which we live, and into ourselves; and what we see is not a picture of a material world, but a world of a new and hitherto unsuspected kind, a world of harmonic vibration, a world of music, a world much less related to matter than to spirit." No longer are these speculations but armchair amusement; mathematical physics is an eminently practical subject as we have all found out.

Before leaving philosophy and settling down to our specific subject, two of many other ways of contemplating the earth and its beings may be mentioned, if only to remind ourselves that we live and work according to some philosophy or other or several of them, even if we do not admit it. The expressions of teleology, though not always designated as such, are used so often that it must be a popular philosophy. But teleology makes the effect resident in the cause; future function determines what happens. In the past and in the present Fate determines the course of events, as illustrated in the famous four opening notes of Beethoven's Fifth Symphony. This is hardly a practical philosophy unless, as Whitehead suggests, the whole cosmos is swallowed up in one grand teleology. As practicing physicians, whether we want to or not, we are definitely concerned with the apparent fact that the effect is resident in the cause. Even if we cannot determine both the speed and direction of an electron, nevertheless we can and do work from and with statistical approximations. When we hear it said that livers were evolved to carry on such and such functions it is a legitimate method of expression, provided we realize the implications which are bound up with the entire history of liver development, differentiation, and function.

Finally the organismal philosophy, as so ably expressed by Whitehead, demands our attention. When two or more units of whatever kind unite, a new entity is produced. The new entity is an organism of its own. It is not a sum of its parts, but acquires new

properties as a result of its wholeness. Its parts fit into and function within it. Cells do not make the organism; the organism makes its cells. Here is a crucial thinking point, and a spring board for experiments in the differentiation and organization problem. Cells appear by multiplication, and at the right times, in the right places, the right cells are produced and fit together to produce a functioning organism, with few exceptions as by mutation, true to the lineage from which the original cell came which started the new organism. An organism is a system devoid of isolated events. Excellent for us physicians, and confounding to the otolaryngologist who sees and knows nothing of a patient except what is above a line across the clavicles, or a gynecologist who looks upon a woman as a uterus, two tubes and two ovaries on a pair of stilts, or an occasional, very rare radiologist who considers nothing except a local area of tumor on which to focus his energy.

Excellent, too, is this philosophy for the biologist, for with its aid he keeps in mind that, dissect and isolate as he must in his experiments, he eventually must fit his findings of separate parts into the whole. But we need not stop here, for even physicists deal with organisms; the atom is certainly not a sum of the properties of its parts, any more than the human body is the sum of the properties of its various chemical elements.

These larger views of nature are mentioned because they condition our approach to all scientific subjects. In particular, the concept of "wholeness" mentioned above has been important in embryology where, as we shall see, there is adequate evidence that the whole has control over its parts to a striking degree. Before entering into this aspect of differentiation let us first consider it in a descriptive sense.

We know that differentiation is a series of processes occurring within a cell or cells, which fits it or them for final function in the whole organism. Many kinds of differentiation are needed, and the progeny of the original cell (the ovum fertilized or otherwise properly stimulated) turn into muscle, nerve, bone, skin, gland, and all the rest.

Differentiation has often been separated from growth by many authors; however, only by the meaning of words. Let us clarify. A narrow concept of the meaning of the word "growth" excludes differentiation. A broader definition includes it, and if growth is defined simply as "increase" a variety of types of increase are suggested:

(1) Increase in size of cells; by increase in number of the same molecules within them, by increase in water content, etc.;
(2) Increase in number of cells;
(3) Increase in chemical diversity of cells. Differentiation begins; cannot be detected visibly;
(4) Increase in structural diversity of cells. Differentiation has proceeded; cells visibly become epithelial, nerve, muscle, etc.;
(5) Increase in functional diversity of cells. Differentiation has reached a point at which the internal set-up is adequate for the cell to start its career in the functioning of the whole organism;
(6) Increase in the organization of cells and tissues into organs and parts. Arms, legs, eyes, livers, are becoming recognizable;
(7) Increase in size, weight, integration, and adaptability to environment of the whole new organism.

The several aspects of growth are not sharply separated at any time in the life cycle of any organism; they overlap, and one after the other temporarily predominates during ontogeny. In repair, replacement, regeneration, the first six are constantly active somewhere and the seventh in addition in unicellular organisms.

Differentiation, then, may be regarded as a form of growth, for it goes on in all of our classifications mentioned above, not excluding cell division itself. When a cell differentiates, it changes its composition, its energy relations and its chemical and physical activities. A whole sweep of events has gone on before we can detect them visibly. These activities then become secondarily mirrored in a changed morphol-

ogy, and the latter state enables us to recognize epithelial, skin, or other types. In groups, differentiation of cells and their arrangement make possible the recognition of tissues, parts and organs, and whether they are normal or diseased. Tumor cell differentiation is both qualitatively and quantitatively different from that of normal cells; indeed, the very statement that such and such tissue is a tumor and not something else depends on abnormal differentiation and recognition that they are not functioning within the framework of the whole. We name tumors from their altered differentiation and then argue about the name, which is good evidence that names are inadequate and are based on insufficient knowledge.

The degree of differentiation is not uniform in every cell in a given tissue. The skin is a good example. As surface cells are shed, a supply of new cells keeps pace by division of incompletely differentiated cells in the basal layers, some of which proceed to differentiation as they migrate toward the surface while others stand at attention, so to speak, as "spare parts" for future need. The more rapid the growth of a tissue the more variety in the degrees of differentiation of the cells present at any one time.

Especially in tumors in which differentiation is disturbed are there variations; the more rapid the increase in mass of a given tumor, the more likely it is to be composed of cells incompletely and more abnormally differentiated. As is well known, degrees of differentiation are potent factors in resistance or sensitivity to irradiation. All of the above is, in its turn, directly concerned with another fact—perhaps as important as any, viz.: differentiation when carried to a particular degree or stage may become an antagonist to cell division. In certain instances when a cell has passed a certain point along its road to differentiation it can no longer divide.

This fact is, of course, of great importance for the cancer problem, for if we can gain enough knowledge of the factors accounting for cell differentiation it might be possible to manipulate them in such a way as to induce differentiation, thereby retarding or stopping cell division in tumors. This is the hope, at least, and although we are still far from having adequate information about the factors controlling differentiation, it would be well at this point to summarize some of the things we do know. These come largely from experimental embryology, and their discovery dates back to the work of the great embryologists—Boveri, Driesch, Morgan, Conklin, Wilson, Harrison, Spemann, and others. One of the first problems approached by these men was the problem of "determination." For example, one might suppose on the one hand that the various parts of the developed embryo are already mapped out in the uncleaved egg, and that differentiation is nothing but an "unfolding" of these parts. Or, on the other hand, it might be supposed that nothing is "determined" at the beginning of development and that differentiation is a progressive process. Unfortunately, there are no means of determining the answer by looking at the cells, or by any known chemical or physical tests. We must observe what they do by deletion or transplantation experiments. When various eggs, such as those of amphibians or echinoderms, are subjected to surgical intervention such as separation of blastomeres or the deletion of parts, there emerges the fact that these eggs will give rise to two or more perfect individuals from separated blastomeres, or will compensate for the loss of a portion of their substance, and the new individual will show no results of its early tribulations. In these eggs the parts are not "determined" to transform into any specific parts of the embryo. They can be exchanged or removed, and the egg will still develop into a whole embryo. These eggs are therefore referred to as regulative eggs.

By contrast, in certain other eggs, such as those of annelids or molluscs, the removal of a part leads to a corresponding defect in the structure of the embryo. Since these eggs seem to be mapped out quite early in development they are referred to

as "mosaic" eggs. Obviously, in these eggs fixed subdivisions have been established for the express purpose of passing on to their descendant cells the starting points for the development of the different tissues, organs, and parts of the new individual. In biological terms the fates of the subdivisions have been determined. In regulatory eggs, on the other hand, subdivisions, if they are there, are interchangeable, determination has not taken place, other parts compensate for the piece removed, and a perfect new individual results. Sooner or later, however, even in the most regulatory of regulatory eggs, the descendant cells can no longer be tampered with without some defect or other appearing. Determination takes place just as it does in mosaic eggs, only later. It seems, therefore, that the difference between regulatory and mosaic eggs in this respect is not a fundamental one, but is a matter of the time at which determination takes place.

What happens when similar procedures are carried out later in development can be illustrated by experiments such as these. A fragment of tissue from the presumptive heart region of a developing amphibian embryo is transplanted to the tail region. It grows into the tissues of the tail. But if the transplantation is done a bit later, the presumptive heart tissue now refuses to become tail and develops into a heart. We thus observe with interest a heart beating in the middle of the tadpole's tail, but no aorta for the heart to pump blood into, perhaps no blood at all.

An even more interesting specimen can be obtained by transplanting cells from the developing eye cup into the abdominal wall. Again, if this is done early the eye becomes transformed into a part of the body wall. However, if it is done a little later the course of development is not changed and the result is an eye looking into a closed abdominal cavity; and apparently trying to watch the movements of the intestines. It sees nothing, of course, for it is dark in the abdominal cavity. The eye is not connected with a brain, but it is an anatomically well developed eye. It reminds us of the famous surrealist painting of a detached eye wistfully contemplating a fried egg in a corner of the picture. Embryos with an accident in their early careers could well be the first surrealists.

From experiments of the type mentioned above we may draw the following conclusions:

(a) The developmental possibilities of a cell are greater than its developmental fate, as in the regulative eggs described above. Incidentally, the human fertilized ovum is on the regulatory side, good evidence for which are the Dionne quintuplets who came from one ovum.
(b) When the fates of a cell and its descendants are determined, it and they will do nothing different; even in an unfavorable environment they will strive hard to fulfill their fate.
(c) The time of determination of the fate of cells varies.

These conclusions may be amplified in the following way—we may say that a cell just born by division of its mother cell has a choice of six alternatives:

(1) To divide.
(2) To remain as is, i.e., undetermined and undifferentiated. In this case its developmental possibilities, that is, its potencies, are greater than its developmental fate will be whenever that is determined. It remains as a "spare part."
(3) To remain undifferentiated for a longer or shorter time even though its developmental fate has been determined. It remains as a restricted "spare part."
(4) To proceed immediately to differentiate into some type of normal cell and fit itself in with the others in the neighborhood, and into an organism of the lineage from which it came.
(5) To mutate, and turn into a cell more or less different from its immediate lineage.
(6) To be determined in an entirely new direction, foreign to the organism and inimical to it, i.e., into a cancer cell.

Translating a few of the above generalities to a situation familiar to us: Have the cells of a growth which we usually call pre-

cancerous—from the piling up of its cells, from their loss of orientation, from their polychromy, from their cytology, but without invasion—really had the potency determined to be cancer cells, and are only awaiting time for their genuine expression, i.e., invasion? Or are they deformed for some other reason than cancer?

We cannot tell from observation alone, and no one would want to take a chance and transplant them into another situation or into another human being, assuming that they would "take"—which is doubtful. This situation has led to such terms as "carcinoma in situ," and the like. They are based on the statistical experience that now and then some lesions labeled "precancerous" do end as invasive cancer. But we would like to know more than statistical experience, and this knowledge must come by way of work on the differentiation problem.

We have stated that the potency or developmental possibilities of, or within, a cell are greater than its normal developmental fate. Obviously, some factor or factors must determine the choice of the potency which is to be expressed. This thought leads directly into the field of the "organizer phenomena" from the biological side, and into such facts as we have of determinants of potencies from the chemical and physical sides; in other words, a study of the factors influencing the choice of potencies of a cell. Observe that we say *choice*, and not potencies themselves—for the latter are undoubtedly resident within cells, and any qualitative change which the environment may cause must act through and within the cells. Many changes such as this lead to the pathological, but as such also come under the heading of differentiation.

Among the factors controlling differentiation we should first mention the "organizer." We have already described the transplantation experiments which showed that early in development, during blastula and gastrula stages, the various parts of the embryo are still not "determined." That is, these parts may be made to differentiate in any direction by grafting them to various sites on host embryos where they will develop in accordance with their new position. However, it was discovered by Spemann, in his work on the amphibian embryo, that there is one very important exception to this rule. The dorsal lip of the blastopore, when grafted to, say, a ventral position on a host embryo, is not moulded into ventral body wall as other parts of the gastrula would be, but rather persists in its normal course. That is, the cells of the dorsal lip roll under the surface of the surrounding ectoderm and there form a sheet of cells—the chorda-mesoderm. Now, Spemann's great discovery was that the dorsal blastoporal lip not only was determined to follow its own course of differentiation, but *in addition* it has the power of organizing the adjacent host tissues into a fairly complete secondary embryo. Thus, the host ectoderm lying above the graft chorda-mesoderm was induced to form brain and spinal cord, the adjacent host mesoderm formed somites and pronephros, and the endoderm beneath formed a gut lumen. Since the dorsal lip appeared thus to have the power of inducing in young embryos the formation of a complete set of axial structures it was called by Spemann the "organizer." It may be mentioned that other regions of the embryo acquire similar powers which they exert on a smaller scale later on in development. Thus the eye is first induced by the organizer (or chorda-mesoderm), but later on it, in turn, is able to induce the formation of lens in the overlying ectoderm.

Soon after Spemann's discovery of the organizer there was a great deal of work done in an attempt to find the chemical nature of the substance or substances that were assumed to be produced by the dorsal lip and to account for its inductive power. For convenience these hypothetical substances were called "evocators" by the English school of chemical embryologists. And since it was known that evocators could only act on undifferentiated cells, and that once acted upon by one evocator the cells lost their capacity to react to

others, the condition of the reactive cells was referred to as "competence." Thus, according to this analysis differentiation requires both a specific chemical substance, or evocator, produced say by the dorsal lip of the blastopore, and a specific sensitivity or competence on the part of the reacting cells—say competence on the part of ectodermal cells to be altered or differentiated into neuroblasts.

Obviously it is of great importance to try to find out the chemical nature of evocators, and to define in chemical terms the condition of competence. Considerable work has been done, but due to certain technical troubles we have not yet succeeded in getting this information for the early and spectacular phases of differentiation in embryos. However, we do have some information for differentiation during later phases of development, and for certain types of recurrent or cyclical differentiation in adults. For example, the feeling of heaviness, the tenderness and the enlargement of the breasts occurring monthly during the reproductive age of menstruating women, are due to hyperplasia of the epithelium at the blind ends of the ductules of the breast. The hyperplasia and subsequent differentiation into ducts and lobules is determined by ovarian hormones circulating within the blood stream. The hormone is picked up by certain breast cells and they respond by hyperplasia and differentiation. Now and again a woman is encountered who has one typical female breast, whereat the other has remained infantile. Obviously, both breast regions have had opportunity to pick up the ovarian hormones distributed through the blood, but only one breast has responded. In the terminology of the organizer, one breast was and the other was not competent to react to the evocator, in this case a hormone. A similar situation exists in the case of the prostate and a number of other tissues sensitive to specific hormones at definite times in their development.

Having discussed the influences which cells and organs exert upon each other during embryonic development, we are in a position to consider the events occurring within the cells during the process of differentiation. Here the interrelations of the different cell structures are central to the theme: the relative roles of nucleus and cytoplasm, the manner in which each influences and is influenced by the other, are the critical problems, problems still at the outskirts of the field.

From the very beginning, genetics, in attempting to understand the resemblances and the differences between members of the same family, found it necessary to postulate that characters themselves are not inherited but must be transmitted by guides or determinants which were found to be in particulate structures within nuclei—and now called genes.

Our knowledge of these units comes from the combination of genetic and cytological study. The genes are arranged in the chromosomes in a linear order, each one having its effect upon a specific character. And most of the hereditary characters that have been studied are controlled by the genes in the chromosomes. There are some exceptions, that have been actively studied in recent years, cases in which the character is controlled by cytoplasmic factors, hence cytoplasmic inheritance. These very exceptions, however, turn out to be manifestations of a common principle, as we shall now see.

The essential characteristic of a gene is the property of self-reproduction, that is, each gene produces more of its own kind. This is the basic fact of inheritance, of course, and in a way of life itself. Now the apparent exception of the cases of cytoplasmic inheritance turns out to be the result of the existence of bodies which have the property of self-reproduction, just as the genes do. In plants, these are frequently the plastids, either green or colorless. In other cases, as in the familiar Paramecium, a type of intracellular virus is the agent. But the major principle, the control of the nature of specific changes in the organism, in other words, the control of types of dif-

ferentiation by the interaction of units of molecular dimensions, is common to all the cases.

We can go a step farther in the assertion of a common basis for biological self-reproduction. We know something about the substances concerned with it, substances found in all the units in which self-reproduction occurs, from the bacterial viruses to human genes. These substances are the nucleic acids, specifically the desoxyribosenucleic acids. These occur in the chromosomes, and uniquely in the chromosomes of cells uninfected with viruses. Where, as in the Paramecium case mentioned above, a virus infection exists, there are particles found in the cytoplasm that contain desoxyribosenucleic acid—DNA for short. Moreover, it has recently been shown that the nuclei of a variety of organisms contain a constant amount of DNA per chromosome set, although the other constituents of the nucleus vary from tissue to tissue. Thus the assurance increases for the idea that the DNA of the chromosomes is essential for the activity and not an accidental part of their structure.

This idea is reinforced by the outstanding example of a specific influence on the differentiation of a single type of cell, the transformation of pneumoccocus from one type to another by a DNA specific for each type. Here the differentiation involves a specific type of substance, the polysaccharide contained in the capsule of the bacillus, and responsible for its type. It seems increasingly clear from this work that the chemists have a new and difficult problem in the analysis of the basis for the specific differences in different DNA preparations.

What are the implications of all this for the problems of differentiation? At each mitosis in development the chromosomes divide, and presumably in the mature cell the amount of DNA is constant per chromosome set; in other words, the implication is that the number of genes is constant. This is a conventional view, one which is only beginning to be tested by experiment. The point to be kept in mind is this, that the methods are just being developed which may allow us to determine whether differentiation involves the genes themselves, and then the cytoplasm, or whether the genes act as the catalysts of differentiation, themselves remaining unchanged throughout the process.

We know that the sizes of nuclei are different in the different tissues, and every pathologist in describing a cell describes its characteristic type of nucleus. How do these changes arise? There is not much analytical work and what there is concerns changes in chromosome size in the nucleus. It has long been known that the early divisions of the egg, from the two to the four cell stage, etc., show a diminution of the size of the chromosomes with each successive cleavage. Does the thesis that has been propounded, that the DNA content of each chromosome set is constant in the species hold here too, even though the size of the chromosome changes? Recent measurements of DNA changes during the early development of the echinoderm egg indicate that the situation is not simple. As the chromosomes decrease in size, the DNA content per cell decreases: so the analysis must now concentrate on the minimal amount of DNA, the lowest common denominator for all chromosome sizes.

What all this means, for our problems of differentiation, appears to be just this: if the DNA content of a chromosome set is proportional to the number of genes, or represents a measure of the number of genes, then the number of genes per cell changes during the cleavage of the egg. This is, of course, a form of differentiation of the nucleus. It may be, and probably is the result of the conditions which the cytoplasm of the egg imposes on mitosis at these early stages of development; but once accomplished, the differentiation of the nucleus is a factor to be studied in the further differentiation of the cytoplasm. And here we must consider what the mode of action of the genes themselves, what the chemical nature of their influence may be.

The visible effects of differentiation in

the cytoplasm are the result of the presence of different substances, all synthesized, in the cases where our information is adequate, under the influence of enzymes. Now the control of these enzymes comes from the nucleus, hence from the genes themselves. And it is an attractive hypothesis that the genes control the specificities of the myriad enzymes needed for the processes of differentiation. The exhaustive work carried on the kinds of enzymes present in the different tissues, what Greenstein calls the enzymatic spectrum of the cell provides concrete evidence that differentiation results in and from the presence of specific groups of enzymes for each type of cell.

Thus, from the nucleus there must appear enzymes in the cytoplasm which, acting upon the materials absorbed by the cytoplasm, guide the formation of chemical substances within the cytoplasm in a given direction. These substances in their turn act on others, both within the cytoplasm and passing through the nuclear membrane to the nucleus, and thus differentiation proceeds. In one sense the cytoplasm acts as the agent of the nucleus. Naturally, it takes some time for the nucleus to express itself through the production of the characteristic modification of the cytoplasm. The length of this lag is variable and experiment has shown it may range from a time shorter than one cell generation to a time longer than the whole life cycle of an organism.

Translated to our above terms, determination corresponds to the time when specific enzymes or their precursors are manufactured by the nucleus and begin to enter the cytoplasm. The variable time between determination and actual differentiation corresponds with the lag time between the beginning of the production of enzymes and their actual activity in the cytoplasm. Differentiation then corresponds to the activity of the enzymes within the cytoplasm rearranging and reconstituting the substances within the cytoplasm to the point of differentiation of the cell in which it takes its place as part of the function of a whole organism. This leaves one, of course, with the question of the mechanism by which the choice is made of the type of enzyme produced by the genes in any particular cell, so that it fits it to function within the whole. We have said that the choice of potency depends upon the environment in the broad sense of the word; thus, materials coming into the cytoplasm play their part in modifying the action of the genes. This beautifully timed and managed reciprocal relation is what constitutes differentiation in its orderly fashion and causes it to function within the whole. Clearly, genes must modify the cytoplasm, and in its turn the cytoplasm must modify the activity of the genes.

The chemical basis of differentiation would therefore appear to lie in the interrelations between nucleic acids or nucleoproteins and the formation of intracellular enzymes.

I cannot let the opportunity pass without mentioning specifically a series of experiments which quite lately have led to what seems a practical application. It concerns the question: How does irradiation in proper dosages stop cell division? An answer in chemical terms to this important question concerns, as one might expect, the same types of substances found important in differentiation.

Some twenty years ago, Hammett in our Institute and Rapkine in Paris showed independently that there was an increase in sulfhydryl groups in dividing cells. Hammett's original question was posed as follows: "What are the chemical differences between cells in division and those not?" In a variety of organisms, starting with peas, beans, corn and onions, he showed that sulfur reduced to sulfhydryl appeared in cells about to and undergoing division. This finding in plants was soon extended to chick embryos, rats, mice, and finally human beings.

It was my good fortune to play a part in the experiments with these latter mammals, and sulfhydryl applied judiciously to wounds increases rates of healing by accelerating cell division. Chalkley and

Voegtlin found the same acceleration in other organisms, including the amoeba. It was shown that if the sulfhydryl group was removed by various chemical means, cell division stopped. Conversely, when sulfhydryl was added, cell division was resumed. Further demonstrations by Hauschka, Swain, Toennies and Briggs showed that the substance, hexenolactone, inhibits cell division by binding sulfhydryl. Its effects could be overcome by the additions of cysteine, a sulfhydryl-containing amino acid to the media. Hexenolactone is mentioned in particular because it was thought to be a differential connective tissue inhibitor, and thus was worthy of trial for its general effects on cell division and its relation to sulfhydryl.

In the beginning the mechanism of the effect of sulfhydryl on proliferation was unknown but was subjected to speculation. Hammett postulated that protein is rearranged during cell division and that various chemical bonds were loosened and severed and that sulfhydryl was responsible for this proteolysis. Barron and Singer have now shown quite impressively that the activities of large numbers of enzymes depend on sulfhydryl groups, i.e., sulfhydryl is a necessary component of the activities of quite a few enzymes. Various organic compounds react strongly and reversibly to sulfhydryl; that is, upon addition of such compounds to a mixture in which the enzyme is acting, the sulfhydryl groups of the enzymes are oxidized and the reaction catalyzed by it is stopped. If now cysteine or reduced glutathione are added to the inhibited enzyme, the sulfur groups of the enzyme are reduced to form sulfhydryl again and the enzyme is reactivated. This information furnished the guide for the understanding of the inhibitory effects of irradiation on cell division.

Barron, Dickman, Pott, Tyree, and others, showed that the sulfhydryl in an enzyme is oxidized by irradiation and therefore inactivated. This can certainly account for at least some of the irradiation damage to animals, for it was found by Potts and coworkers that by injecting cysteine, but no cystine, there was a reduction of at least 60 to 65 per cent in the mortality of rats given lethal body doses of radiation. While it seems certain that the immediate damaging effects of irradiation can be partially prevented, it remains to be seen whether later effects are also under control of the sulfhydryl groups restored by injecting cysteine. Its effects on human beings remain to be discovered, but it seems a reasonable lead to try.

These effects on enzymes do not complete the roster of the effects of irradiation. One of the salient changes, relevant to our earlier discussion of the nucleic acids and differentiation, was found by Mitchell. His experiments showed an accumulation of nucleic acid in the cytoplasm of irradiated cells, concomitant with the inhibition of mitosis. Remembering that at mitosis there must be a synthesis of desoxyribosenucleic acid, Mitchell postulated that the effect of irradiation was to destroy or inhibit the enzyme having to do with this synthesis. Thus the accumulation of nucleic acid in the cytoplasm (ribose nucleic acid) resulted from the use of the substrates made available by blocked reaction of desoxyribosenucleic acid formation in the nucleus.

Thus, what might be a primary effect of irradiation on the enzyme produces secondary effects on such substances as the nucleic acids and these, as we have mentioned above, may be important in the synthesis of a variety of enzymes. So we again see that the biological effects of irradiation are very complex, and in order to be understood will involve the best efforts of both the practical and experimental workers.

All of the above are familiar thoughts to a worker in the study of cancer. The fundamental questions are not difficult to see, if we but remember that differentiation is perverted in the tumor cell; that cancer cells do not become organized in the production of organs and parts which function within the framework of the

whole. Now, wherein lie the changes expressed in chemical and physical terms?

* * *

I began the discussion this evening by a reference to underlying *philosophical* systems, and tried to carry a particular theme throughout—namely, the necessity for regarding the organism as a whole and I would like to close with a few more remarks along a quasi-philosophical vein, particularly on the necessity of hypothesis.

Upon reflection, the importance of the contributions of such men as William Harvey, Charles Darwin, and Gregor Mendel—to mention but a few of the great biologists—consists not so much upon the observations they made in the field and in the laboratory, but in the new hypotheses which they introduced. These were the stimuli to magnificent subsequent development. Their hypotheses indicated an order in a previous chaos, and not only were new facts uncovered but whole new branches of science were created. In the field of growth and development, men like Conklin, McClung, Hertwig, and Spemann introduced a number of new hypotheses, perhaps of a less high order, it is true, but nonetheless stimulative of a huge flow of new knowledge. During the past fifteen or twenty years apparently no new hypotheses of like order have been introduced in the field. The time is ripe for new ones to again set in motion a whole screed of new experiments. There are some who say that the development of instruments has led to new results and finer details. With equal assurance it may be stated that the development of new hypotheses leads to the development of new instruments, designed especially to test the hypotheses. Unlike the development of the fission bomb—which had behind it numerous fundamental discoveries and extensive and far-reaching hypotheses—embryology and the growth and development problems seem to be in need of further discoveries, based on sound far-reaching hypotheses. Especially is this so in the cancer problem, the core of which is, as in normal growth and development, the differentiation of cells.

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THE QUANTITATIVE DETERMINATION OF GAMMA RADIATION IN BIOLOGICAL RESEARCH*

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THE detection of gamma radiation emitted by radioactive isotopes as a means of determining the presence and concentration of a given isotope in different media presents a variety of problems. These differ widely depending upon the radiation characteristics, the nature of the source to be measured and the level of activity. Further complications, particularly in the case of measurements in vivo, are caused by the presence of radioactivity in locations other than the one of immediate interest. Sometimes, only relative values are sufficient—either for the same source at different times or for different sources relative to some standard. In other cases, mainly where roentgen dosage determinations are required, absolute values of the radioactivity are necessary.

The most common instrument in use for the detection of the gamma radiation emitted by radioactive isotopes is the *Geiger-Müller counter*. For a given source strength, one must consider on the one hand, the total number of gamma rays emitted per unit time and, on the other, the registered number of counts. The latter is usually only a small fraction of the total source emission. This fraction is a function of the relative position and sizes of source and counter, of the absorption by all intervening media including the source itself, and of scattering. All these factors may be grouped together under the term *geometry*. The registered number of counts depends not only upon the geometry but upon the inherent *sensitivity* of the counter. The sensitivity of the counter is defined as the ratio of the actual number of counts to the number of incident gamma rays. For the most efficient use of a Geiger counter in any given situation, both the sensitivity and geometry must be carefully considered.

SENSITIVITY OF GEIGER COUNTERS TO GAMMA RADIATION

Gamma radiation can trigger a Geiger counter only by producing secondary electrons. This conversion takes place chiefly in the walls of the counter by means of photoelectric emission, Compton scattering and pair production. In each case, the probability of occurrence is a function of the electron density of the walls and the quantum energy of the gamma rays. The detection of the secondary electrons depends upon their range since they must leave the walls and enter the sensitive volume of the counter. By taking these factors into consideration, Bradt and coworkers[3] have plotted the expected sensitivities as a function of quantum energy for counters whose inside walls consist of aluminum, brass or lead (Fig. 1). The experimentally determined sensitivities for the gamma radiation of In^{111}, C^{11}, Al^{28}, Mn^{56} and ThC″ agree with the calculated

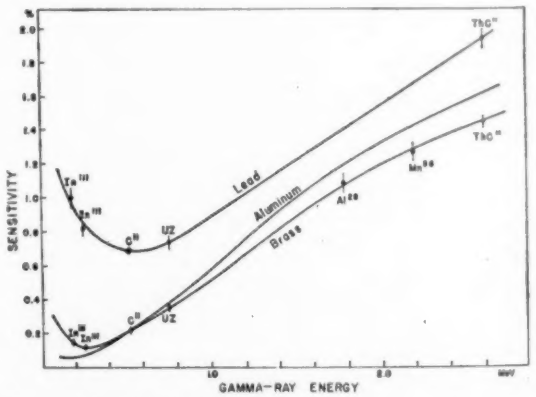

FIG. 1. Sensitivity of Geiger-Müller counters as a function of gamma-ray energy (Bradt *et al.*).

* This work was supported by the Office of Naval Research under Contract N6-ORI-99.
† Now at the Argonne National Laboratory, Chicago, Illinois.

curve. As an example of the order of magnitude to be expected for a lead counter, Bradt's curve shows that from 500 kev. to 2 mev., the sensitivity increases nearly linearly from 0.7 per cent to 1.6 per cent.

To increase the low sensitivity of conventional counters in the above energy range, attempts have been based upon a multicellular type of design, i.e. a series of counters in parallel. This increases the metallic volume in which energy conversion can occur without increasing the thickness through which the secondary electrons must pass before they enter the filling gas. In one type described by Beyster and Wiedenbeck,[2] each cell consists of two parallel brass disks as the cathode and a circular wire midway between the disks, as the anode. Twelve such cells connected together are reported as giving 10 times the usual gamma-ray sensitivity. In a recent variation of this method, Slätis[12] uses systems of concentric rings. A tube consisting of an assembly of 22 parallel ring systems, each with 3 concentric rings, is stated to have a sensitivity 2.5-3.2 times that of a Geiger-Müller tube of the same size for the gamma radiation of Ra, Co^{60} and Hg^{203}.

A tube similar in principle to the ones just described, has been in use in this laboratory since 1946. This tube consists of a series of parallel metal plates as the cathode and a series of parallel wires passing through holes in the plates, as the anode.* Used end-on as described below, the sensitivities to the gamma radiations of I^{131}, Co^{60} and Ra were found to be two to three times higher than those given in Figure 1.

Although special designs have effected some improvement, Geiger tubes are limited in their sensitivities to gamma radiation. In this respect, the *scintillation counter*[8] has theoretically a distinct advantage. Instead of a gas-filled tube, this device consists of a solid crystal. The absorption of gamma rays occurs by the same processes as in the walls of a Geiger counter. The secondary electrons produce fluorescent radiation, characteristic of the crystal. A photomultiplier tube is used as the detector for this radiation. The important difference between the Geiger tube and the crystal is that the latter can be made thick enough to increase the absorption of gamma radiation while at the same time it remains *transparent* to its fluorescent radiation. In this way, the inherent sensitivity should approach 100 per cent.

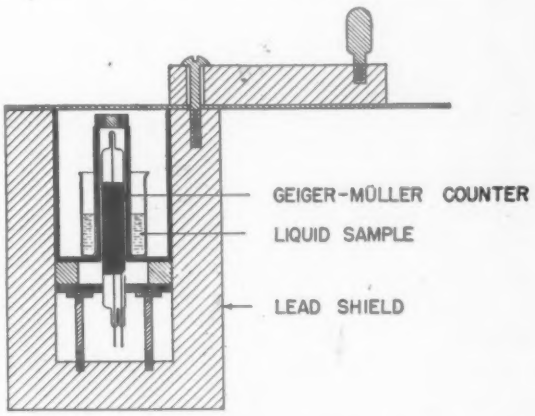

Fig. 2. Arrangement for counting gamma rays from liquid samples at nearly 2π geometry.

Measurement of Liquid and Dried Samples

In most situations in which the activities of liquid or dried samples are to be measured, only relative values are required and comparisons are made between the counting rate of the sample and that of a standard prepared in the same way and measured in the same position. In general, for maximum efficiency, it is desirable to use as large a solid angle as possible. If the source is a *liquid*, arrangements can be made to give nearly 2π or 4π geometry, depending upon whether the sample surrounds the counter or vice versa. This is shown in Figures 2 and 3. In Figure 1, 2π geometry is achieved by surrounding a conventional glass cylinder type of Geiger counter with the sample. The sample holder is a glass beaker with a hole in its base. A section of glass tubing, long enough to serve as a handle also has been blown into the hole so

* A more complete description is given in U. S. Patent No. 2,397,661. (April 2, 1946).

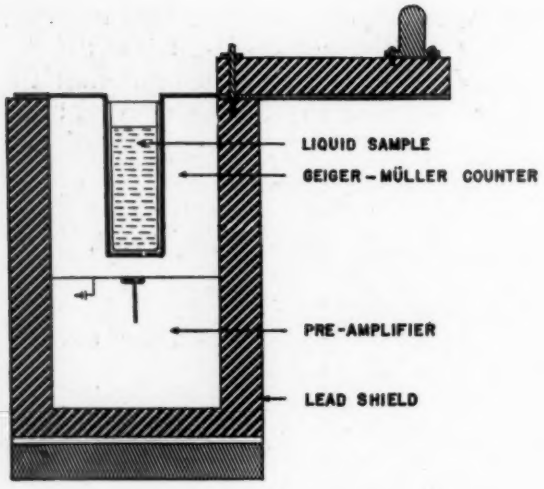

FIG. 3. Arrangement for counting gamma-ray samples at nearly 4π geometry.

that the beaker can be slipped over the counter.*

In Figure 3, nearly 4π geometry is obtained by surrounding the sample with the counter. The Geiger counter is a specially designed tube obtained from the Texas Company,† of similar internal construction to the one described above. However, it is shaped so that the sample within a flat-based glass cylinder can be placed inside it. In both arrangements shown, the counters are protected from contamination in case of spillage, by removable brass envelopes. In addition, the entire apparatus is lead shielded to reduce the background counting rate. Good geometry can also be achieved by connecting conventional counters in parallel and spacing them in a circle around the source.[13]

If the source is a solid, the counter must be at a distance such that the entire source is within the solid angle subtended by the shielded counter. This eliminates errors due to and inhomogeneous distribution of radioactivity. If the source area is small in comparison with the area of the counter, it can be placed as close to the latter as conditions permit. However, the most satisfactory arrangement should allow variability in the distance between the sample and the tube so that high levels of activity can be measured without recourse either to dilution of the sample or to waiting for sufficient radoactive decay.

* This equipment, first designed by one of the present authors (L.D.M.) and in use in this laboratory since 1943, can now be obtained from Technical Associates, Inc., Glendale, California.

† A more complete description is given in U. S. Patent No. 2,397,661. (April 2, 1946).

MEASUREMENT OF RADIOACTIVITY IN VIVO

The use of radioactive iodine (I^{131}) as a tracer for the study of thyroid physiology,[10] a therapeutic agent in the treatment of hyperthyroidism[4,6] or thyroid carcinoma[11] and a localizer of brain tumors,[9] provides good examples of problems encountered in measurements in vivo. Therefore, the I^{131} gamma radiation will be used to illustrate a counting technique which also applies to other gamma-ray emitters.

Counter Shielding. The concentration of I^{131} may be very high in regions of the body other than the one of immediate interest. Therefore the entire counter exclusive of its aperture should be shielded[5] so that a mini-

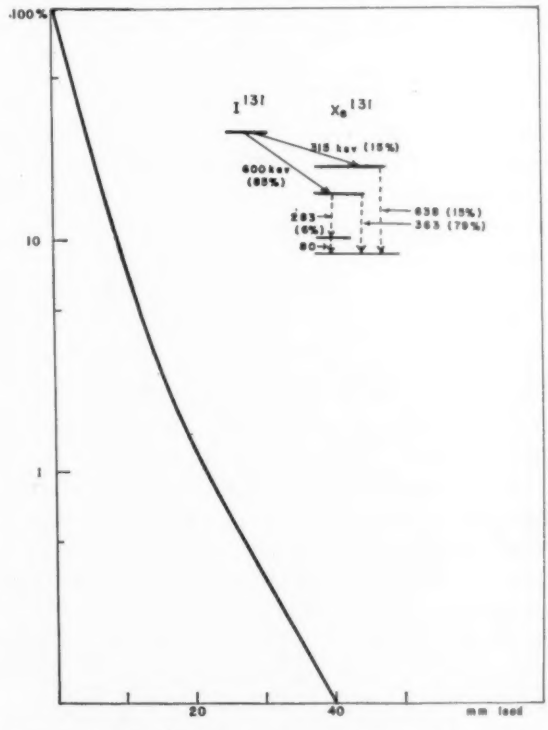

FIG. 4. Disintegration scheme for I^{131} and absorption curve for its gamma radiation in lead.

mum of radiation can enter from other directions. The amount of shielding required for the I^{131} gamma radiation can be obtained from Figure 4. This shows its disintegration scheme[7] and the calculated total gamma-ray absorption curve in lead. It can be seen that, in order to reduce the incident intensity to less than 1 per cent, about 22 mm. of lead are needed. Figure 5 shows the shielded counter used in this laboratory; the actual lead thickness is 25 mm.

Background. In spite of shielding, the level of activity to be measured may still be comparable to the background counting rate. This situation occurs when the administered dose of I^{131} is very small, or the retention by the given area is poor. It is also the case when the administered dose is large but measurements are taken at a time when the blood activity is still high and the activity in the region of interest has not yet reached its maximum. To correct for this high background, it is convenient to make measurements with a lead plug, fitting into the aperture of the shielded counter. The difference between readings taken with and without the plug gives the activity of the source plus the fraction of body background radiation which is also included within the solid angle subtended by the shielded counter.

The thickness of the lead plug should be sufficient to cut out the radiation from the source as completely as possible. The plug used for the counter of Figure 5 is 32 mm. thick. According to the absorption curve of Figure 4, this will reduce the intensity to 0.3 per cent, which is adequate for most situations.

High Counting Rates. When the counting rate exceeds the limit set by the resolving time of the counter and scaling circuit, an intermediate lead filter will reduce it. The thickness of this filter must be less than that of the lead plug by which the background is determined. It is useful to have available, filters of different thickness for different levels of activity. When the source activity decays to a point where unfiltered readings may be taken, those readings taken with a filter can be translated into unfiltered readings by a proper conversion factor.

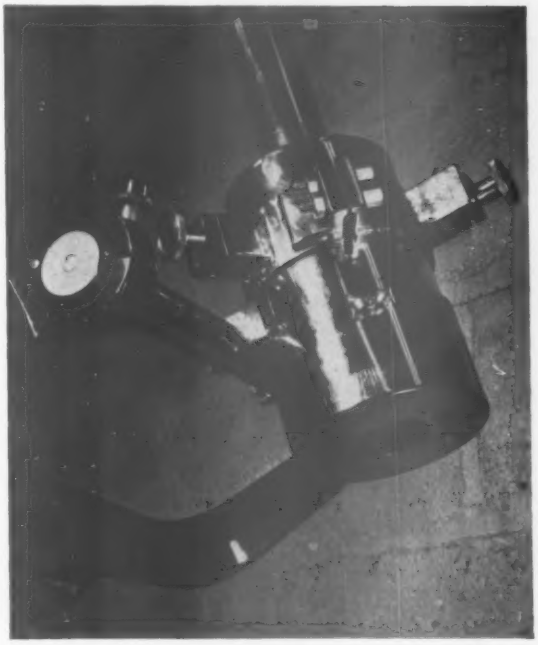

Fig. 5. Lead-shielded Geiger counter, with preamplifier projecting in back. The extension of the shield in front defines the aperture.

Counter Calibration. When the percentage of an administered dose of I^{131} retained in either the thyroid gland or in a functional tumor is desired, the registered counting rate must be translated into millicuries* of activity, i.e. the counter must be calibrated. As in the case of dried samples, inhomogeneity of distribution of I^{131} requires that measurements be made at such a distance that the entire source is "seen" by the counter. This distance should be the smallest at which the source relative to the counter is effectively a point since, at larger distances, the amount of radiation from other sources included within the solid angle of measurement, increases. Furthermore with increasing distance between counter and source, the reproducibility of readings improves since an inaccuracy in

* The I^{131} calibration was based on its gamma-ray output of 2.35 roentgens per millicurie-hour at 1 cm. from a point source.

placing the counter will be only a small fraction of the total distance.

The distance in question is the total distance from the center of the source to the effective center of the counter. Unfortunately, in most practical situations, the position of the center of the source (thyroid gland or tumor) cannot be determined easily. Therefore it must either be estimated or measurements must be taken to its front surface. The effective center of the counter may not coincide with the geometrical center but can be determined experimentally. If C is the distance from the end of the counter to its effective center and D is the distance from a point source to the same end of the counter, the inverse square law is expressed as counting rate $= \frac{(\text{constant})^2}{(C+D)^2}$. From this equation, it follows that

$$D = \frac{\text{constant}}{\sqrt{\text{counting rate}}} - C.$$

By using a small source of I^{131} and plotting $\frac{I}{\sqrt{\text{counting rate}}}$ as a function of D, C is obtained as the negative intercept on the D-axis.

The determination of the optimum distance for thyroid gland measurements was carried out by using the glands of 9 patients scheduled for total surgical thyroidectomy and the tube shown in Figure 5. Two millicuries of I^{131} were administered by mouth forty eight hours before operation. At five hours or less before this time, the activity of the gland in each case was measured at total skin*-to-center of tube distances ranging from 17 to 32 cm. The excised gland was placed in a glass beaker and its activity remeasured at the same distances, this time measured to the front edge of the beaker.† These measurements were repeated for a solution containing a standardized I^{131} activity in a beaker of the same size. The solution was made up to a volume approximating that of the gland in each case.

Each patient was checked for completeness of thyroidectomy three to four days after surgery. Residual neck activity was found in only one case and correction was made for it. Thus for each patient, three sets of readings were obtained: (*a*) for the gland in vivo, (*b*) for the gland in vitro and (*c*) for a known I^{131} activity in a volume approximating that of the gland in vitro.

TABLE I

INVERSE SQUARE LAW VARIATION FOR I^{131} SOLUTION IN GLASS BEAKER

Patient	$I \cdot d^2$ at			
	17 cm.	22 cm.	27 cm.	32 cm.
L.C.	89	96	100	100
S.K.	91	94	96	100
P.D.	89	95	97	100
C.K.	76	91	101	100
M.A.	93	99	98	100
E.G.	82	90	93	100
J.R.	100	100	105	100
P.M.	89	93	99	100
L.A.	85	92	96	100
Average	88 ±5	95 ±3	98 ±3	100

Table I shows the inverse square law variation for case (*c*)—the I^{131} solution in the different glass beakers used for the different patients. The data shown were obtained by multiplying the counting rate by the square of the distance and then dividing this value by the value obtained at 32 cm., which was taken as 100. It can be seen that, on this basis, the average deviation was 12 per cent for a distance of 17 cm. but dropped to 5 per cent at 22 cm.

In Table II, the reading for (*b*)—the gland in vitro is compared with (*c*)—the I^{131} solution in a similar beaker and the results were also normalized at 32 cm. On the average, these checked to within 3 per cent for all the distances considered. Only for

* The area of skin was over the isthmus of the thyroid.

† The beakers used for the different patients ranged in volume from 100 to 400 ml.

TABLE II

COMPARISON OF THYROID IN BEAKER WITH I^{131} SOLUTION IN BEAKER

Patient	Gland Weight* (grams)	Ratio of $\frac{\text{Thyroid Reading in Vitro}}{I^{131}\text{ Solution in Beaker}}$ at			
		17 cm.	22 cm.	27 cm.	32 cm.
L.C.	20	112	112	107	100
S.K.	40	98	100	102	100
P.D.	170	83	84	88	100
C.K.	78	98	93	93	100
M.A.	100	82	94	100	100
E.G.	12	101	102	103	100
J.R.	2	101	106	93	100
P.M.	60	100	102	94	100
L.A.	55	96	100	103	100
Average		97 ±7	99 ±6	98 ±6	100

* Except for the 170 gram gland, the weights were calculated from the dimensions supplied by the surgeon or the pathologist. The 170 gram gland was weighed.

the two largest glands at the shorter distances was the deviation considerably larger. This was probably due to the inhomogeneous distribution of I^{131} within the tissue. One may conclude that the error involved in comparing the gland in a beaker with an I^{131} solution in a beaker of the same size is less than the error caused by deviations from inverse square law conditions, i.e.where the source is not effectively a point.

In Table III, the reading for the gland in vivo is compared with that for the gland in vitro. In general, the ratio between these readings increases with distance. The reading in vivo may be as much as 50 per cent higher, due to the increasing contribution of radiation from that portion of the body,

TABLE III

COMPARISON OF THYROID IN VIVO WITH THYROID IN VITRO

Patient	Gland Weight (grams)	Ratio of $\frac{\text{Thyroid Reading in Vivo}}{\text{Thyroid Reading in Vitro}}$ at			
		17 cm.	22 cm.	27 cm.	32 cm.
L.C.	20	0.93	1.00	1.06	1.21
S.K.	40	0.87	0.97	1.02	1.06
P.D.	170	1.00	1.07	1.10	1.03
C.K.	78	1.08	1.11	1.11	1.11
M.A.	100	1.25	1.21	1.11	1.14
E.G.	12	0.99	1.16	1.27	1.38
J.R.	2	0.96	1.19	1.49	1.46
P.M.	60	1.10	1.26	1.37	1.33
L.A.	55	0.85	0.95	1.03	1.11
Average		1.00 ±.09	1.10 ±.09	1.19 ±.14	1.20 ±.13

included within the solid angle of measurement.

On the basis of the values in Table III, the optimum distance at which measurements should be taken is 22 cm. or less. However, Table I showed that at 17 cm. there was significant deviation from the inverse square law. Therefore 22 cm. was considered to be the distance which best satisfied all requirements.

From the above considerations, the tube calibration at 22 cm. was finally obtained as

$$\text{counts/min/}\mu\text{c in vivo} = \frac{\text{counts/min in vivo}}{\text{counts/min in vitro}} \times \text{counts/min/}\mu\text{c of } I^{131}$$

solution in beaker. The calibration factor for the given tube, averaged for the 9 glands, was 20 ± 2 counts/min/μc in vivo. Considering the errors involved in the factors on the right side of the equation, the error in any determination of the number of microcuries in a given gland, was estimated to be of the order of 15–20 per cent.

Measurement of Tumors Containing I^{131}. The extension of the method described above to the case of tumors containing I^{131} is a difficult matter, in general. For single small tumors situated very near the surface of the body or at a known depth and which concentrate large amounts of I^{131}, the method can be applied directly. If the tumor is at an appreciable depth, a correction to the value of the counts/min/μc in vivo should be used to account for the absorption of the radiation in the overlying layers of tissue. This correction can be obtained by determining the percentage reduction in the counting rate of a given source due to a thickness of pressed wood equal to the tumor depth.

The concentration of I^{131} in most functional tumors is higher than that in the blood but much less than that found in the thyroid. Therefore, the amount of radiation from the rest of the body entering the aperture of the counter is a much higher fraction of the total radiation detected. In order to correct for this high background, it is necessary to take a control reading over an analogous part of the body. If the tumor is very large, it may be impossible to measure its activity at a distance sufficient to include all of it, without measuring a considerable amount of radiation from the rest of the body as well. Even if such a distance were practical, it is likely that at an equal distance from the control area, part of the radiation from the tumor will also be measured. In such a case, one has no alternative but to take readings with the counter in contact with the skin and be contented with relative values. However, if a biopsy is possible, one can obtain a factor relating the counting rate at the skin surface to the tumor concentration of I^{131}.

Further difficulties are encountered in the case of tumors situated in the midline of the body. Here there is no suitable control area in the same region, which is equidistant from the neck and from the midline. One procedure in this case is to take readings over areas to the right and left of the tumor, equidistant from its center or outer borders, and to use the average of these readings as a control. Here again, error may be introduced by including radiation from the tumor at either or both of these supposed control areas, if the tumor is extensive and located at an appreciable depth.

It is important to emphasize at this point that the proper interpretation of in vivo measurements requires a knowledge of time variations in activity for different regions of the body to be expected for normal individuals. Such information is still rather scanty but absolutely necessary if one has to decide whether activity and turnover rate in a given region are normal or due to a functioning tumor. In the case of the bladder, for instance, the background will be high during the first forty eight hours after a dose is administered. In questionable situations, readings should be repeated after the bladder has been emptied. An-

other example is the stomach where normal changes in readings depending upon the presence of water, food or both, require study.

Resolution of Sources. The counter shielding discussed above allows a single source to be measured in the presence of a diffuse distribution of radiation. However, the measurement of tumors which are very near other sources of activity such as the thyroid, bladder, stomach or other tumors, requires in addition an appropriate resolving power of the counter.

The angle at which unfiltered gamma radiation entered the tube in the experiments above was limited by the short extension of the lead shield projecting from the end of the tube as shown in Figure 5. Figure 6 shows an arrangement for varying this angle. The results obtained for three different settings are shown in Figure 7. A 3 ml. source of I^{131} in a small glass bottle, 1.5 cm. in diameter, was kept at a fixed distance D from the end of the counter but moved along a line perpendicular to its axis. The curves below show the variation in intensity as a function of lateral displacement of the source from the axis. In the first case A, the counter was flush with the end of the lead shielding. The corresponding curve A shows how, for this situation, appreciable activity was still detected at large distances from the counter axis. At 8 cm. e.g., the intensity fell to only 50 per cent. In case B, the lead shield has a fixed extension in front of the tube (as in Fig. 5) and a movable diaphragm (Fig. 6). The total length of projecting lead tubing is indicated by L. The width of the corresponding curve B is considerably smaller than that of A. When in case C, the diaphragm was moved close to the source, the width of the curve did not markedly exceed the geometrical opening.* It can be seen that the width of the curve is not primarily dependent upon the distance between the source and the proximal end of the diaphragm, as soon as L is an appreciable fraction of D.

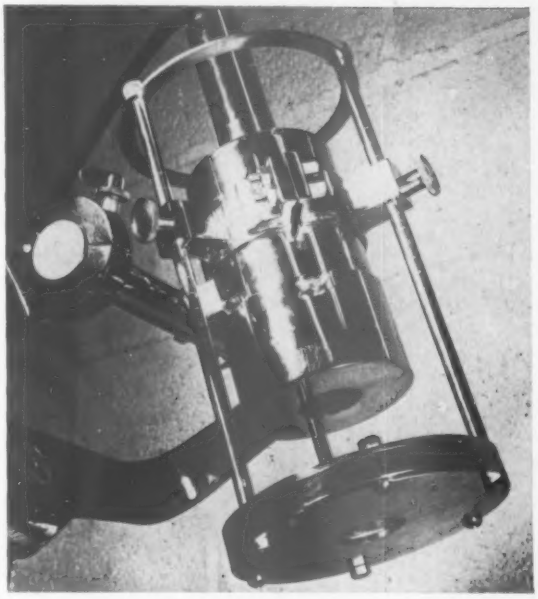

Fig. 6. Lead-shielded Geiger counter equipped with movable lead diaphragm for varying the size of the aperture.

From the above discussion, it is evident that two sources will be completely resolved if their centers are farther apart than 16 cm. in case B and 7 cm. in case C. If further resolution is required, the diameter of the aperture must be reduced.

The resolving power does not depend on whether the distance L is defined by a movable lead diaphragm as shown in Figure 6 or a solid lead cylinder. In the case of a solid lead cylinder, some radiation scattered from its walls may be detected. However, measurements with I^{131} and the tube of Figure 5, gave about equal counting rates with both methods. This indicates that the scattered gamma rays produced by soft primary radiation were not detected. For harder radiation than that of I^{131}, this may not be the case. In this respect, the diaphragm method has an advantage and in addition it avoids a considerable weight of lead. On the other hand, the diaphragm has the disadvantage of requiring a large outside diameter to prevent radiation from entering through the air gap between the two sections of the apparatus.

* A curve similar to C was obtained by Ansell and Rotblat.[1] These workers used a solid lead cylinder instead of a diaphragm. A point source at 2.5 cm. from the end of the cylinder was moved in the same manner as described above. Their calculated curve, assuming complete absorption of gamma rays, originating outside the geometrical aperture agreed with the experimental curve.

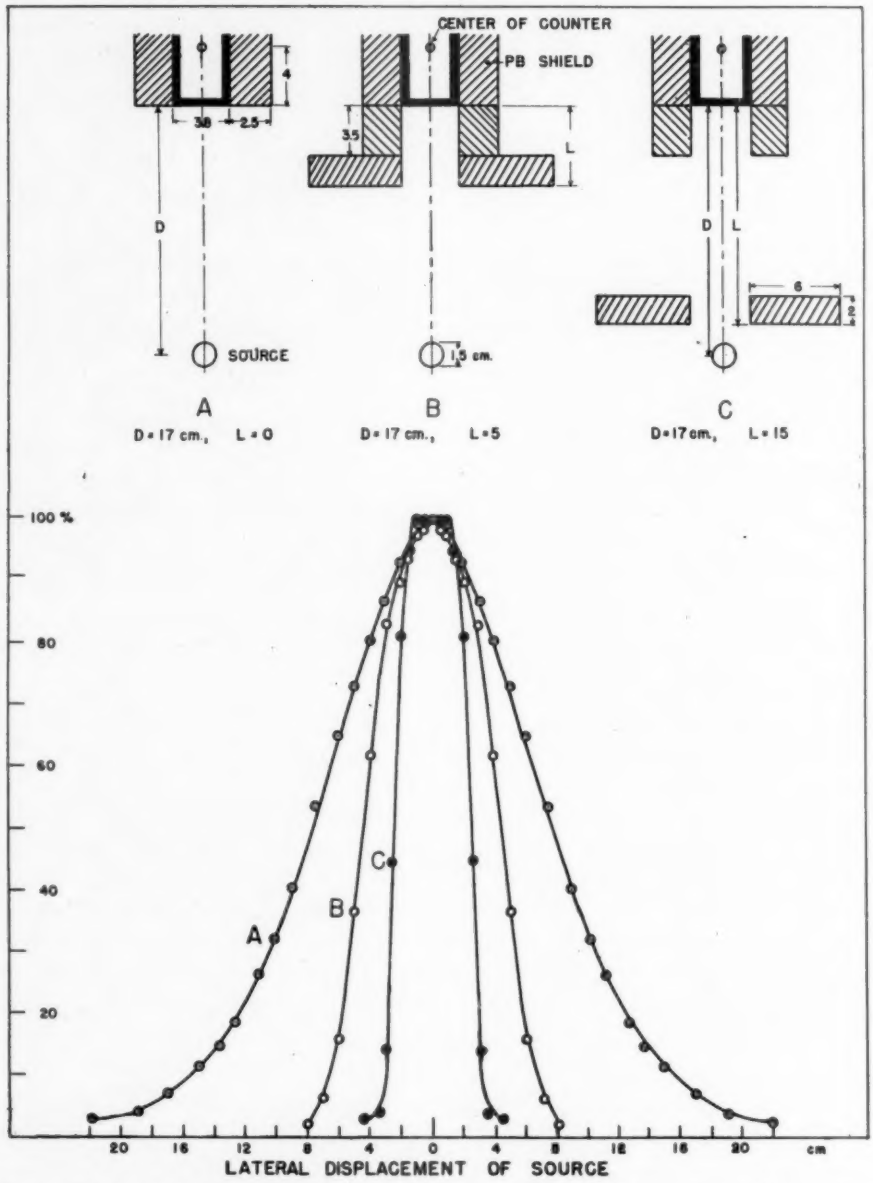

FIG. 7. Variation in counting rate as a function of lateral displacement of counter or source for different values of *L*.

SUMMARY

The quantitative determination of gamma radiation depends upon the sensitivity of the measuring device and the physical conditions under which it is used. The limited sensitivity of the Geiger counter has been discussed and the advantage of the scintillation counter, in this respect, has been pointed out.

I^{131} has been used to illustrate the physical problems involved in the in vitro and in vivo measurement of gamma radiation. Apparatus for achieving 2π and 4π geometry in the measurement of liquid samples has been shown. Improvements in the technique employed for in vivo measurement consist of lead shielding and lead plugs. An apparatus combining these features and the calibration of this apparatus for quantitative use with the thyroid gland have been

described. The latter feature requires the determination of an optimum skin-to-counter distance such that most glands will be effectively point sources and such that the measured fraction of body background radiation will be minimal.

Difficulties encountered in the measurement of the gamma rays from thyroid tumors are due to tumor size, poor collection of I^{131}, anatomical location and the proximity of other tumors. The problem of resolving different sources of activity has been analyzed and shown to be dependent upon the angle subtended by the counter. This aperture can be defined either by a movable lead diaphragm or a fixed lead cylinder, depending upon the specific problem.

We are indebted to Mr. C. F. Teichmann and Dr., G. Herzog of the Texas Company for the counting equipment donated to us. We also wish to express our gratitude to J. Heslin, A. Emory, R. Kulin for technical assistance, M. Berman for valuable suggestions, and M. M. Elkind for the construction of the lead shielding and diaphragm.

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RADIOBIOLOGICAL ADDITIVITY OF VARIOUS IONIZING RADIATIONS*

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STUDIES on additivity of radiations† are of interest for two reasons. First, in practical radiobiology, it is important to know, under conditions where more than one type of ionizing radiation may be encountered, whether all types add to produce injury or whether attention should be focussed only on the one which is present in greatest radiobiological intensity. Second, and more important in the long view, additivity studies provide basic information about mechanisms of action of radiations.

Additivity studies are not a new invention; they have been used in radiobiology for at least two decades, the earliest record I have found being a paper published by Quimby in 1927. (This will be discussed later.)

The general technique for testing the additivity of two radiations A and B (e.g., gamma rays and fast neutrons) may be illustrated by reference to Figure 1. A definite qualitative biological effect is selected for study, in this case the well known inhibition of hatching of *Drosophila* eggs. Samples of the biological object are exposed to graded doses of each radiation, and dose-effect curves are obtained by plotting degree of effect (e.g. percentage hatching) against dose. From these curves one can read off the dose of each radiation required to produce some convenient degree of effect such as 50 per cent hatching. Let us call such a dose a definitive dose. Now it is to be noted that the two definitive doses thus determined, regardless of their physical magnitudes and of the units in which each is expressed, are *radiobiologically* equal. Accordingly if the two radiations are radiobiologically completely additive, one-half of a definitive dose of radiation A plus one-half of a definitive dose of radiation B should produce the same degree of effect as a definitive dose of either radiation applied separately. The same is true of any two partial definitive doses, such as one-third of A plus two-thirds of B, provided that the sum of the two is one definitive dose. On the other hand, if the two radiations are not at all additive, the effect of two partial definitive doses will be equal in effectiveness only to the partial dose which by itself produces the greater effect. There is also an intermediate possibility, namely that the two radiations are incompletely additive, in which case the effect of the partial definitive doses is greater than that of either of the partial doses taken alone but less than that of one full definitive dose of either radiation.‡

Now let us consider some results of additivity studies, beginning with the case already mentioned—inhibition of hatching of *Drosophila* eggs.[6] From inspection of Figure 1 it is evident that the definitive dose for 50 per cent inhibition is 86 rep (roentgen equivalent physical) of fast fission neutrons or 240 roentgens of gamma rays. Six combinations of partial definitive doses were tested. For instance, in one test 56 per cent of a definitive dose of gamma rays (135 r) was added to 44 per cent of a definitive dose of fast neutrons (37.5 rep). The percentage inhibition of hatching was exactly 50 per cent. In the other five tests it was respectively 51.0,

† This paper is concerned only with studies on ionizing radiations. Literature on effects of non-ionizing radiation, such as ultraviolet and infrared, combined with ionizing radiations is not considered here.

‡ There is the still further possibility that the effect of the partial doses may be greater than that of one definitive dose—that is, the radiations may be more than additive—but this has not, so far as I know, ever been observed.

* Presented at the Forty-Ninth Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 14–17, 1948.

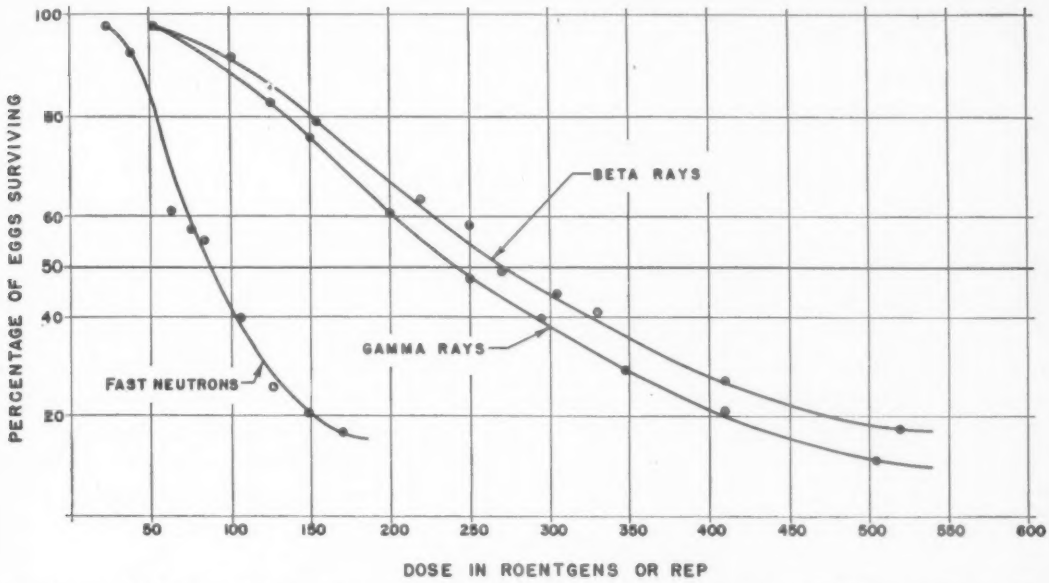

FIG. 1. Survival of *Drosophila* eggs exposed to graded amounts of P^{32} beta rays, Ta^{182} gamma rays and fast fission neutrons. (The fast neutron exposures were measured in n-units and converted to roentgen equivalent physical (rep) by the relation 1 n-unit equals 2.5 rep.) Data from Stapleton and Zirkle.[6]

TABLE I

SUMMARY OF VARIOUS ADDITIVITY STUDIES

Radiations Tested	Biological Object	Biological Effect	Degree of Additivity	Authors and Date
Gamma; fast neutron (doses delivered in about 1 hour)	Mouse	Death in 30 days	Complete	Zirkle, Raper, Riley and Stapleton,[8] 1945
Gamma; fast neutron (doses delivered in 24 or 48 hours)	Mouse	Death in 21 days	Incomplete	Mitchell,[2] 1947
X; alpha	Bean root	Stoppage of growth	Nearly complete	Gray and Read,[1] 1944
Beta; gamma	*Drosophila* eggs	Inhibition of hatching	Complete	Stapleton and Zirkle,[6] 1946
Beta; fast neutron				
Gamma; fast neutron				
Gamma; roentgen rays (200 kv.)	*Drosophila* pupae	Inhibition of hatching	Complete	Müller,[3] 1939
Beta; gamma	Mouse	Death in 45 days	Incomplete	Raper and Barnes,[5] 1947
Beta; gamma	Human skin	Threshold erythema	Incomplete	Quimby,[4] 1927

50.4, 50.6, 50.2 and 45.0 per cent, all of which values match the theoretical value of 50 per cent within the experimental error. It is accordingly evident that, in producing inhibition of hatching of *Drosophila* eggs, gamma rays and fast neutrons are completely additive. Still further tests showed that beta rays (P^{32}) and fast fission neutrons were also completely additive, as well as beta rays and gamma rays.

The foregoing results are summarized in Table 1, along with those of the other experiments to be discussed.

Some years before the studies on *Drosophila* eggs just mentioned, J. H. Müller[3] tested gamma rays and 200 kv. roentgen rays for additivity in inhibiting the hatching of *Drosophila* pupae. The two radiations proved to be completely additive.

A similar result was obtained by Gray and Read,[1] who tested the additivity of 180 kv. roentgen rays and alpha rays from radon and its decay products in solution. The biological object was the root of the broad bean, and the effect studied was lethal action as evidenced by permanent stoppage of growth. The unanalyzed data indicate that the two radiations were almost but not quite completely additive, but the authors' analysis of the sources of error in the experiment shows that the deviation from complete additivity is probably not real. A similar result was obtained in less extensive tests with gamma rays and fast neutrons.

All of the experiments so far mentioned have been performed on small biological objects, and in all cases, within the experimental errors, the additivity has been complete. The remaining experiments to be discussed were performed on mammals, and here the picture is not so uniform.

Let us first consider experiments in which the entire body of the animal was exposed uniformly to both types of radiation used. During the war the radiobiological group at Clinton Laboratories, Oak Ridge, tested the additivity of hard gamma rays and fast fission neutrons in producing death of mice within thirty days after irradiation.[8] The two radiations were additive within 7 per cent, which is well within the experimental error. Quite different results were obtained by Mitchell,[2] who studied death of mice within twenty-one days after irradiation and tested the additivity of hard gamma rays and fast neutrons from a polonium-beryllium source. The experimental error was large but there seems to be no room for doubt that the two radiations were only partially and far from completely additive. The reason for the discrepancy is not the criterion of effect, since the mortality within twenty-one days is practically the same as within thirty days. Moreover, the gamma rays used in the two investigations were very similar in physical properties, and although the fast neutrons differed somewhat in their energy spectra, this seems insufficient to account for the great difference in the degree of additivity observed. On the other hand, there was a marked difference in technique of delivering the radiations. In the Oak Ridge experiments, all doses were delivered in times of the order of one hour; in Mitchell's the exposures lasted either twenty-four or forty-eight hours. It is to this difference in timing of the irradiations that the discrepancy in additivity is probably due, and this circumstance makes it appear highly probable that, in their acute lethal action on mice, gamma rays and fast neutrons operate through the same mechanism when the length of exposure is short but at least partially through different mechanisms when the exposures are long. Moreover, the difference in results of the two sets of experiments strongly indicates that the lethal effects of the short exposures and the long exposures are brought about at least partially by different mechanisms.

A radically different type of additivity study was carried out by Raper and Barnes[5] at Oak Ridge. The acute lethal actions of beta rays (P^{32}) and hard gamma rays were tested on mice. The gamma rays irradiated the entire body, whereas the beta rays irradiated only the external few millimeters over the entire surface of the

body. The additivity turned out to be about half complete—that is, the effectiveness of a full definitive dose of either radiation was matched only by using three-fourths of a definitive dose of each radiation, applied simultaneously. In view of the great difference in distribution of the tissue doses of the two radiations, it is not surprising that the additivity is only partial. On the other hand, it is very interesting that these radiations add to the extent observed.

We now come finally to the earliest additivity studies to be considered. In 1927 Quimby[4] described experiments in which the threshold erythema in human skin was produced by gamma rays, by a lightly filtered radium emission which was predominantly beta, and by combinations of the two. The two radiations added only incompletely despite the fact that the sources were so arranged that the depth dose curves were practically identical to a depth of 1 centimeter, which is somewhat greater than the range of the beta rays. The failure of these two radiations to add completely is very surprising, because the ionization tracks produced are very similar in properties. The only obvious physical difference between the gamma and the beta exposures is the depth dose beyond 1 centimeter, and this seems to be a very unlikely factor to which to ascribe the marked incompleteness of additivity. Indeed, these erythema experiments are the only ones I know in which a failure to add is not accompanied by some obvious major physical difference in the irradiations. Perhaps the future will furnish the missing information.

Let us now see what conclusions can be drawn from all the available data. Let us consider the group of investigations[1,3,6,8] in which additivity was complete. It will be noted that in all these cases the gross distribution of ionization or absorbed energy was identical, in fact uniform, for each pair of radiations tested because in all cases the radiation was either quite penetrating or was emitted by uniformly distributed radioactive substances. This probably goes far toward explaining the complete additivity. On the other hand, most of the pairs of radiations tested differed widely in the microscopic distribution of the ionization. This was particularly true of beta, gamma or roentgen rays vs. fast neutrons or alpha particles, because the members of the first group, directly or indirectly, produce electron tracks, along which the ions are formed relatively sparsely—that is, the specific ionization is low—while the members of the second group produce, directly or indirectly, tracks of light atomic nuclei, along which the ions are formed densely (specific ionization high). In numerous investigations,* including those discussed here, it has been found that usually the radiations producing high specific ionization are several times as effective per unit dose as those producing low specific ionization; and this naturally has aroused the suspicion that perhaps the mechanisms of action might be different and that some evidence for this might be obtained by additivity studies. This is certainly not uniformly true. Of the pertinent investigations with radiations differing greatly in specific ionization, only Mitchell's reveals a lack of complete additivity.

At this point it might be well to inquire how much we can deduce concerning radiobiological mechanisms from the results of additivity tests. It is commonly considered that, between the moment of irradiation, with the production of ionization tracks and the absorption of energy, and the time of observation of the biological end effect, there intervenes a series of events which are relevant to and lead to the effect observed. The number, natures and sequence of these events are not yet known for any biological effect. Such a sequence of relevant events may, however, be visualized somewhat as follows:

$$\text{Irradiation} \rightarrow A \rightarrow B \rightarrow C \rightarrow E,$$

where A, B and C are successive unknown relevant events and E is the known biological effect, which is usually of the all-or-

* Many of these have been recently reviewed.[7]

none type. C may further be designated a *determinative* event, in the sense that, when it has occurred a sufficient number of times in the biological object, the effect E will ensue even though still other events must furnish a transition from C to E.

Now, if two radiations both produce the effect E by exactly the sequence of events just given and by no other, they must be completely additive in a radiobiological sense, even though their effectiveness per unit of energy absorbed might be widely different.* On the other hand, the converse is not necessarily true—that is, complete additivity does not prove that the mechanisms are identical. It merely proves that the determinative event C is qualitatively the same for both radiations. For example, the two may have mechanisms as follows:

(Radiation I) Irradiation→A→B→C→E
(Radiation II) Irradiation→A→B′→C→E,

where events B and B′ are not identical but both lead to event C.

Complete additivity accordingly requires that the determinative event C be identical for both radiations. Obversely, complete lack of additivity requires that the mechanisms of the two radiations be unlike and unrelated in the ways in which they lead to the end effect E. This situation would be illustrated by the scheme shown in the preceding paragraph if, in the sequence for radiation II, B′ led to a determinative event C′ which is unlike and independent of C but which leads to E if sufficiently numerous in occurrence. It is to be noted that none of the experiments described here resulted in complete lack of additivity.

Partial additivity, on the other hand, is observed quite commonly among the available investigations. It may be explained in two ways: (1) The mechanisms of the two radiations may have different determinative events C and C′, but, instead of being completely independent, they are related in their ability to determine the effect E.† (2) The mechanisms of radiations I and II may have different and completely independent determinative events C and C′ respectively, but radiation II also produces some events C in subdeterminative amounts —that is, the events C′ are produced in sufficient numbers to cause the end effect E by a dose smaller than needed to produce enough events C to cause E.

The foregoing remarks may be summarized as follows: *Incomplete* additivity of two radiations indicates *some* difference in mechanism. *Complete* additivity indicates that the mechanisms are identical in their most essential feature—the determinative events—but not necessarily alike otherwise.

From the practical standpoint of radiation hazards it would seem at present, despite one investigation on mammals[2] which indicates only partial additivity of gamma rays and fast neutrons, that it probably would be wise, pending information on more kinds of biological effects, to assume the worst possible situation, namely complete additivity.

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* Such a difference could be ascribed, for instance, to the production of different numbers of event A, due, for example, to differences in ion distribution. A difference in numbers of event A would of course be reflected in different numbers of the determinative event C and hence in different efficiency in producing the effect E.

† For instance, E might be inhibition of cell division, C the destruction of the molecules of an enzyme and C′ a decrease in pH due to formation of hydrogen ions. Either C or C′ could cause inhibition of cell division (E) after definitive doses of radiations I and II respectively, but neither alone could cause it after half a definitive dose. After half a definitive dose of each, the radiations would appear to be partially additive if the change in pH (event C′) decreased the activity of the enzyme molecules not destroyed via event C.

Considerations of this sort could of course qualitatively explain not only partial additivity but also complete additivity. However, to obtain complete additivity by such a combination of two mechanisms would require such especially complementary properties of the two dose-effect curves that the probability of such a result would appear to be extremely small.

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SOME BIOLOGIC EFFECTS OF LONG CONTINUED IRRADIATION*†

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IT IS well known that absorption of ionizing radiation by tissues is connected with damage, however small the dose. In addition, exposures over years may be cumulative to a varying degree. With the ever increasing number of scientific and industrial workers who are subjected to exposures to ionizing radiations the need for an extensive study of the biologic effects of exposures to radiations becomes of increasing importance. The question arises whether or not a daily minimum or "permissible" dose for man can be established from experimental data for whole body chronic irradiation of animals. We would define such a dose as one which, when given over considerable periods of time, cannot be expressed in pathologic changes. The damage may, however, result in shortening of the life span of the individual; this shortening should be very small and of insignificant percentage. The "permissible" dose of 0.1 roentgen per day was based on scientific data wanting in completeness. It is obvious that as long as data are not available on man, we have to be guided by findings in experimental animals. To explore the biologic effects in experimental animals in the range of the "permissible" dose in their broadest aspects, an exhaustive study was begun at the National Cancer Institute early in 1941, greatly expanded during World War II, and is still continuing. Some of the results obtained will be reported in the following.

METHODS

The experimental animals were mice, guinea pigs and rabbits. The exposure was started when the animals were mature and was continued during the entire life span. Autopsies were performed on each animal. Whenever possible animals were killed when in extremis instead of waiting for their death. As roentgen machines obviously are not well suited for daily eight hour exposures to small doses extending over years, gamma radiation from radium was used for such exposures. Besides requiring little space, once calibrated, only routine checks on the dose delivered are necessary. In addition, the greater penetrating power of the gamma rays will give more uniform tissue doses in small animals than is possible to obtain with roentgen radiation produced by standard machines.

Three gamma radiation sources were used: 1 gm., 250 mg. and 100 mg. filtered by 0.5 mm. of platinum. The experimental arrangement has been described in detail elsewhere.[1] The animals were placed at equal distances from the source for each given intensity level. By dose measurements in each cage, corrections in source distances due to absorption and scattering were made. Dose levels were 8.8 r, 4.4 r, 2.2 r, 1.1 r and 0.11 r given in eight hours per day.

With such small daily doses animals will stay in good health for considerable time and quite large doses can be accumulated before death occurs. This gives the opportunity to study progressive changes over long periods. To give an example: for guinea pigs the LD50-30 day dose is approximately 300 r when given in a single acute dose, while the mean lethal dose for chronic exposure to 4.4 r given in eight

* Presented at the Forty-Ninth Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 14–17, 1948.
† The work reported herein was done at the National Cancer Institute as part of the program of the Metallurgical Laboratory, University of Chicago, under the Manhattan Project and is also based on work performed under Contract W-31-109-eng.-38 for the Manhattan Project of the Argonne National Laboratory.

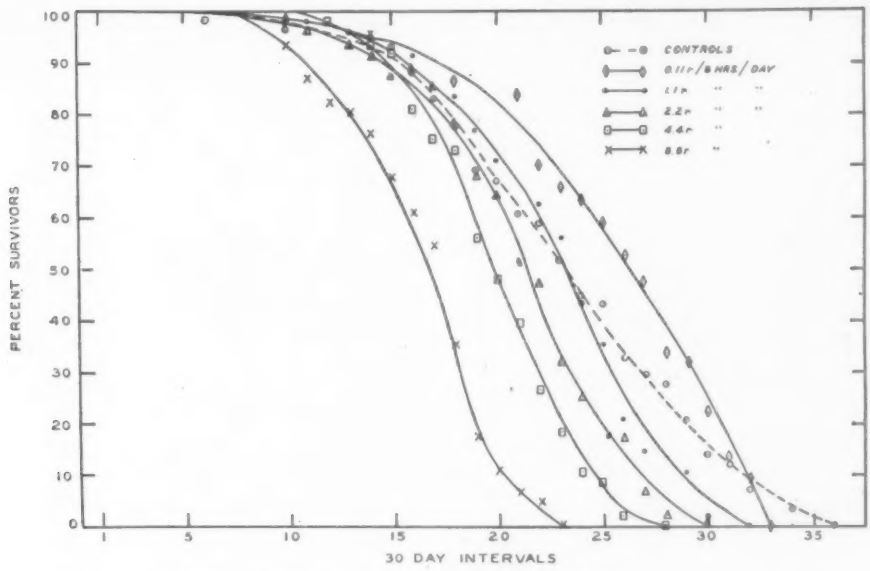

Fig. 1. Percentage of surviving mice vs. time.

hours per day is approximately 2,900 r, which corresponds to a mean survival time of 650 days from the start of exposure.

RESULTS

A. Survival. The effect on the life span is shown in mortality curves. Figure 1 gives the mortality curves for mice. The mice used were genetically homogeneous LAF_1 hybrids obtained by mating strain A fathers to strain L mothers. These hybrid mice were chosen in preference to inbred mice because they are more vigorous, have a longer life span and are relatively free of spontaneous degenerative diseases. The curves of Figure 1 reflect the injurious action of chronic irradiation. From the survival data the mean survival time and the mean accumulated dose can be derived (Table 1). These data indicate a linear relationship between mean survival time and mean accumulated dose (Fig. 2).

The mechanism of death following chronic irradiation is not the same for all species. In mice, shortening of life span is in part due to increased tumor incidence and in part due to unknown effects, and there is no pronounced radiation injury syndrome in mice, notably no terminal anemia or leukopenia, when exposed to the dose level of these experiments. A completely different picture, however, is found in guinea pigs. Radiation death in most of the animals exposed to 8.8 r, 4.4 r and 2.2 r given in eight hours per day is due to pancytopenia. The guinea pigs used in these experiments are genetically heterogeneous hybrids. Figure 3 gives the mortality curves. They show that there is no

Table I

Mean survival time and mean accumulated dose of LAF_1 mice

Number of Animals	Dose Level (r)	Mean Survival Time (days)*	Mean Accumulated Dose (r)†
45	8.8	488	4300
48	4.4	591	2600
47	2.2	630	1400
48	1.1	684	775
45	0.11	761	107
59	Controls	703	—

* Data on mean survival time are significant only in the 8.8 r to 2.2 r groups.

† Mean accumulated doses in the 0.11 r group are somewhat higher than doses calculated from mean survival time as some animals of all groups received additional acute exposures of 12.5 r or 50 r respectively. These additional exposures had no effect on the mean survival time even in the 0.11 r group.

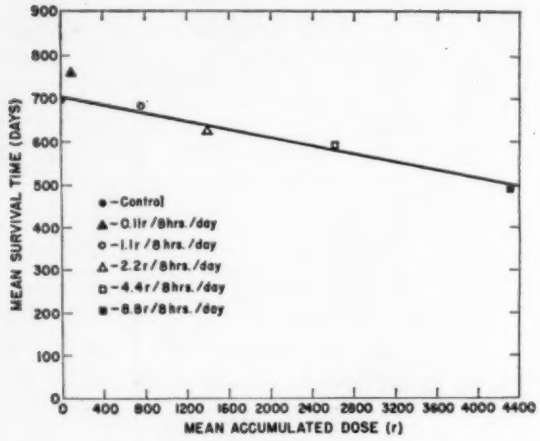

FIG. 2. Mean survival time vs. mean accumulated dose for mice.

TABLE II

MEAN SURVIVAL AND MEAN ACCUMULATED DOSE OF HYBRID GUINEA PIGS

Number of Animals	Dose Level (r)	Mean Survival Time (days)*	Mean Accumulated Dose (r)†
18	8.8	187	1700
18	4.4	653	2900
18	2.2	987	2200
17	1.1	1335	1400
17	0.11	1457	180
24	Controls	1400	—

* Data on mean survival time are significant only in the 8.8 r to 2.2 r groups.

† Mean accumulated doses in the 0.11 r group are somewhat higher than doses calculated from mean survival time as some animals of all groups received additional acute exposures of 12.5 r or 50 r respectively. These additional exposures had no effect on the mean survival time even in the 0.11 r group.

decrease in life span of the animals exposed to 0.11 r in comparison to the control animals. However, the number of animals used on each dose level is small and the fact that no difference in life span on this level is observed does not mean that no difference will be found if a large number of animals is used. On all other exposure levels there is a considerable reduction in life span. While the majority of the guinea pigs exposed to 8.8 r, 4.4 r and 2.2 r died of pancytopenia, no radiation death from this syndrome occurred in the 1.1 r group, indicating that here repair processes balance injury as far as the hematopoietic system is concerned. Therefore radiation death from pancytopenia is a function of dose rate rather than total dose, and no linear relation exists between mean survival time and mean lethal dose (Table II).

Too few animals were used in the experi-

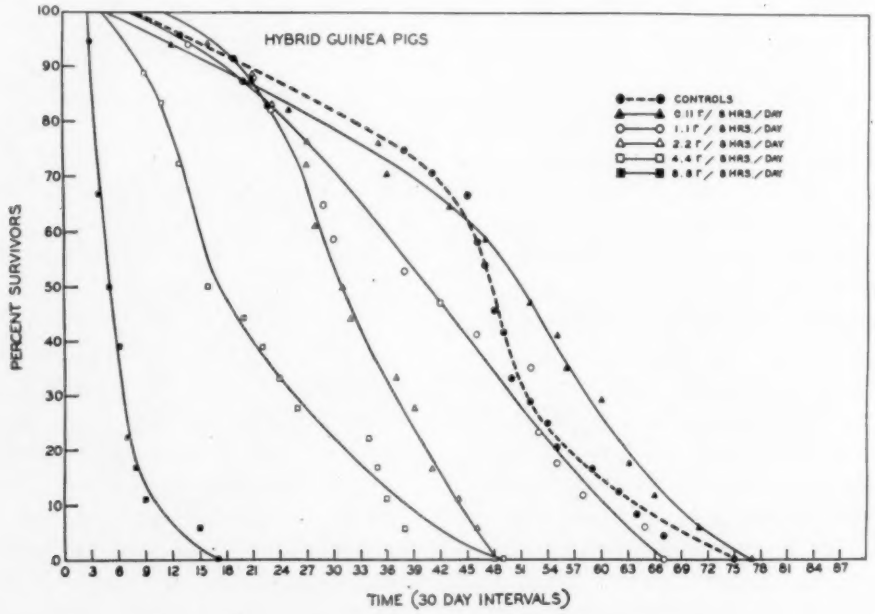

FIG. 3. Percentage of surviving guinea pigs vs. time.

ments with rabbits to obtain survival curves. The hematopoietic system of rabbits is not very radiosensitive, and no death from pancytopenia occurred in these animals under the irradiation conditions of the experiments.

While the response of the hematopoietic system of all species is qualitatively similar following acute exposures in the LD50-30 days range, this dose differs considerably for the three species, being approximately 300 r for guinea pigs, 600 r for mice and 800 r for rabbits. This most likely explains the striking differences encountered in the three species when exposed chronically to the dosage rates used in our experiments.

B. Carcinogenesis. A more complicated picture presents itself in evaluating the carcinogenic effects of penetrating radiation in chronic exposures. With the exception of lymphoid tumors in mice, induction of tumors by irradiation is characterized by a long tumor development time. This indicates that the earlier in life exposure begins, the greater the possibility of tumor development for a given accumulated dose. Usually, tumors induced by irradiation also occur spontaneously but irradiation causes them to appear at an earlier age and in a higher incidence than they ordinarily would without exposure. Generally, with the few quantitative data that have been accumulated, the dosage rate seems to be more important than the total dose.

The carcinogenic action is most readily observed in mice because (1) they are more susceptible to tumor formation than any other species, and (2) the tumor development time is shorter in mice than in animals with a longer life span. But tumors induced by whole-body irradiation were found in all three species, and there is no reason to believe that other species as well as man will be exempt from this action of radiation.

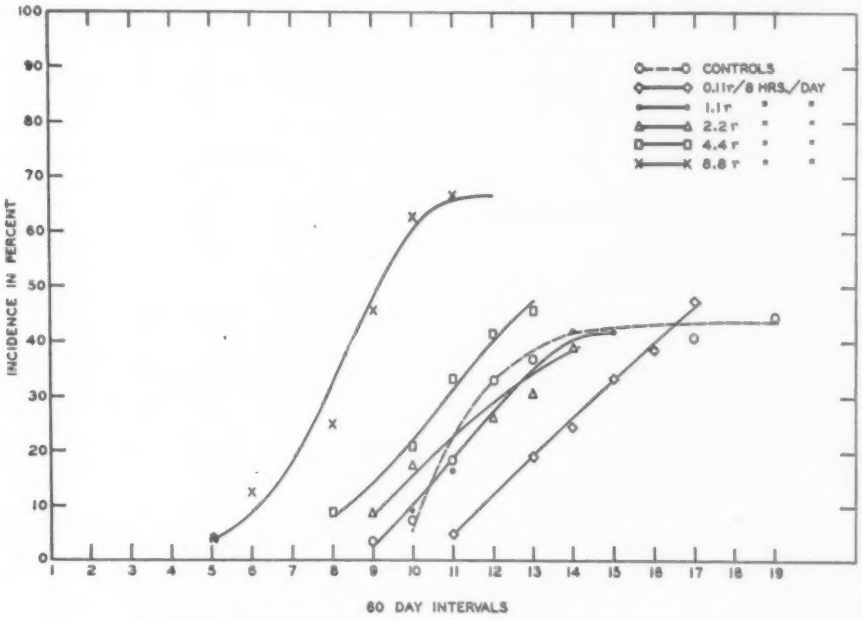

Fig. 4. Percentage incidence of leukemia in female mice.

1. Lymphoid Tumors. Most strains of mice develop a certain percentage of leukemia mainly of the lymphoid type during their life span. The nonirradiated mice used as controls for the animals which were chronically exposed showed an incidence of approximately 50 per cent in the females and 10 per cent in the males. Incidence data for the females of all groups are given in the accumulated incidence curves of Figure 4. The curves show that

the mean tumor development time and the incidence for the 2.2 r, 1.1 r and control groups are approximately the same within the limits of biologic variation. The curve for the animals exposed to 4.4 r indicates a shift toward earlier tumor development time, and this shift is pronounced in the 8.8 r group in which, in addition, the incidence is 20 per cent higher than in the other groups. The conclusion may be drawn that chronic irradiation of these mice after they have reached maturity does not alter to a great extent the over-all incidence but mainly the time at which the tumors appear. This indicates a dependence upon dose rate rather than total dose. It was noted that most of the early tumors of the 8.8 r group were of thymic origin. Another experiment lends support to this observation. Newborn mice of strain A, a strain that has a low incidence of spontaneous leukemia, were exposed to a single acute dose of 400 r of roentgen radiation. Lymphoid tumors mainly of thymic origin developed in approximately 25 per cent of the animals up to the age of seven months; from then on no additional lymphoid tumors were observed to the age of twelve months, when the experiment was terminated (Fig. 5). In strain A mice exposed to gamma radiation at the rate of 8.8 r given in eight hours per day an incidence of lymphoid tumors of approximately 6 per cent was observed. These mice had received a total accumulated dose of approximately 2,500 r (ref. 2).

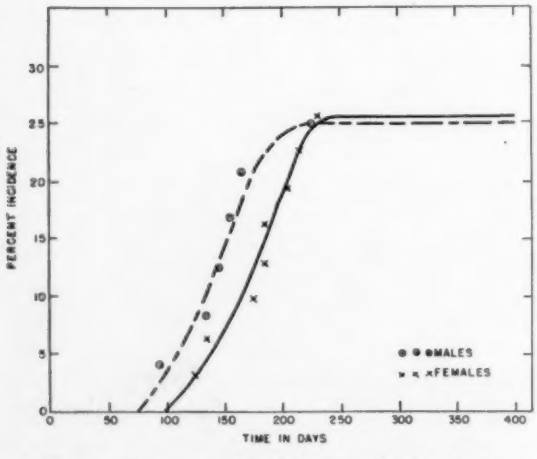

Fig. 5. Percentage incidence of leukemia in mice irradiated at birth.

Kaplan[3] employed C57 black mice in a bioassay and histopathologic study of various lymphoid structures at serial intervals following fractionated whole-body roentgen irradiation and found that lymphoid tumors developing in young mice of this strain regularly made their first appearance in the thymus gland. He also found[4] a marked age factor; for the same total dose the incidence of lymphoid tumors in strain C57 black mice was an inverse function of the age of the animals. Thus the following conclusions may be drawn: (1) that young, growing animals are most susceptible to radiation induced leukemia whether the radiation is given acutely or chronically at the rate of 8.8 r and perhaps 4.4 r given in eight hours per day, (2) that chronic irradiation at lower dosage rates does not materially influence the spontaneous incidence and tumor development time, and (3) that tumors induced by irradiation seem to arise primarily in the thymus. This last conclusion is strongly supported by the findings of Furth[5] who showed that thymectomy effectively decreases the spontaneous incidence of leukemia in his AK strain of mice. Kaplan* found the same to hold true for leukemia induced by irradiation.

The age dependence of lymphoid tumors raises the question whether the process of induction is a direct (local) effect of the irradiation on the thymus or an indirect (systemic) effect. It is known that the thymus reaches its maximum size in growing, not fully mature animals. This age period is also a time of intense endocrine activity. Both of these factors may explain the age dependence of the incidence of lymphoid tumors but do not reveal whether or not a systemic effect is involved. Recent experiments by Kaplan[6] give considerable support to the view that a sys-

* Unpublished data.

temic effect is involved. He irradiated only the upper half or lower half of the body of strain C57 black mice with the same dose of roentgen radiation used in whole body irradiation of other mice (1,000 r in 10 divided doses). The incidence of lymphoid tumors in the groups that received part body irradiation was found to be about 3 to 5 per cent, which is spontaneous incidence. On the other hand, the group receiving the same dose over the whole body had an incidence of 60 per cent. All groups were of the same age when irradiated. Finally Lorenz and Eschenbrenner* observed the development of lymphomas with thymic involvement in strain A mice (exposed to 750 r of roentgen radiation in 10 divided doses at the age of two months) irradiated over the entire body with the thorax (and thymus) shielded. The incidence was significantly increased but somewhat lower than that noted with whole body irradiation. Thus the available knowledge points strongly to a systemic effect of the irradiation. The opinion prevails that tumor induction is caused by a direct effect of the irradiation on the tissues involved. While this probably holds generally for other tumors the data presented indicate that an interaction between systemic and local effects may be involved in lymphoid tumor induction by irradiation to a greater degree than is realized.

The induction of leukemia in mice caused by either acute or chronic whole body irradiation with penetrating radiations seems to be a peculiarity of this species. Guinea pigs also develop spontaneous leukemia at several years of age; the spontaneous incidence, however, is small. In 70 nonirradiated control guinea pigs (both hybrids and inbred strains) 3 cases of spontaneous leukemia have been found thus far, and in 200 guinea pigs exposed to chronic irradiation, only 2 cases were observed although the majority of these animals accumulated doses of between 1,000 r and 6,000 r. No leukemia was observed in rabbits irradiated with similar doses; however, the number of animals used in these experiments was small.

It is interesting to speculate by extending these experimental findings in the three species to radiation induced leukemia in man. Statistical evidence has been brought forth in the literature[7,8,9] which indicates that more radiologists succumb to the disease than other physicians. Comparing the irradiation conditions that induce leukemia in animals to those that the radiologist is exposed to, the following facts are found. Chronic irradiation produces leukemia in mice only when young animals are exposed chronically to a dosage rate to the whole body far exceeding that which the radiologist encounters in roentgenoscopic work. In addition, roentgenoscopy involves only part of the body; such exposure in mice, as mentioned, has only a negligible effect on leukemia incidence. Furthermore, the radiologist is exposed mainly to soft radiations so that the average tissue dose is very small in comparison to the skin dose, whereas in mice the tissue dose is uniform and approximately equal to the air dose. Finally, in guinea pigs, in which the spontaneous incidence of leukemia is small, no evidence has been found to indicate that long continued irradiation will increase the spontaneous incidence. In spite of the statistical evidence reported, the data obtained in experimental animals do not seem to support the view that chronic irradiation will induce leukemia in man unless one is willing to assume differences in the susceptibility and the mechanism of leukemia induction in humans.

2. Lung Tumors. Lung tumors occur spontaneously in a number of strains of mice. They are of alveolar origin, develop slowly, and rarely cause death. Hence incidence data in experiments covering the whole life span are merely suggestive. To obtain quantitative data, an experiment was performed in which mice of strain A, which is the most susceptible strain known, were exposed chronically to an accumu-

* Unpublished data.

lated dose of approximately 2,500 r given at the rate of 8.8 r in eight hours daily. Non-irradiated controls and the irradiated animals were killed at approximately eleven months of age.[2] Seventy-five per cent of the irradiated animals showed lung tumors as compared with 45 per cent of the non-irradiated group. This result as well as the finding of an increase in the number of lung nodules in the irradiated animals is highly significant. The question arises whether a systemic effect produced by the whole body irradiation may play a role in the induction of these tumors. An experiment* was performed in which three groups of mice of the same age were given whole body irradiation with roentgen radiation (750 r in 10 divided doses). One group received whole body irradiation; in the second group the lungs were exposed while the rest of the body was shielded, and in the third group the lungs were shielded and the remainder of the body was exposed. Data obtained thus far indicate that lung tumors are induced by a direct effect of the irradiation on the lung and that no systemic effect is involved.

3. Mammary Tumors. Most interesting has been a study of the effect of long continued whole body irradiation on tumors of the mammary gland of mice.[10] Three causal factors are known in the genesis of these tumors: a genetic factor, a hormonal factor, and the milk factor which is probably a virus. There is good evidence that the LAF_1 mice used in the chronic experiments do not carry the milk factor or carry only a very weak milk factor. Neither the control group nor the group exposed to 0.11 r given in eight hours per day developed mammary tumors. In all other experimental groups receiving daily exposures of 1.1 r to 8.8 r, such tumors occurred with an incidence ranging from 4 to 14 per cent. Since the number of animals in the different groups was small and the incidence comparatively low, it was decided to repeat this experiment with a larger group of animals exposed to 8.8 r given in eight hours per day. Strain C_3Hb mice were used as experimental animals. Mice of this strain were derived by caesarean section from mice of the C_3H strain, which carry the milk factor and were foster nursed by a mother of the C57 black strain, which is free of the milk factor. Ninety-six female mice were exposed beginning at one month of age, and the exposure was continued throughout the life span. The highest accumulated dose was 5,900 r. A total of 23 per cent of the animals developed mammary carcinoma, with a mean tumor age of fifteen months. In 16 virgin controls no mammary carcinoma was found. However, Heston[11] reported a 24 per cent incidence of mammary tumors with an average tumor age of sixteen months in intensely bred females of the same strain. No evidence of the milk factor was found in these breeders nor in the irradiated animals. Tests for the milk factor by preparing and injecting of cell free tumor extracts into newborn mice failed to show the presence of the milk factor. This, however, cannot be taken as absolute proof that the agent is not present, especially since considerable quantities of the agent are destroyed in the preparation of the extract.

The striking difference in these two experiments, although they give comparable results, lies in the relative hormonal activity of the intensely bred and irradiated groups. Intense breeding causes a considerable hormonal stimulation. Numerous experiments have shown that chronically irradiated mice are sterilized by a total accumulated dose of approximately 900 r. Sterility is apparently associated with a reduced estrogen output, and yet, despite the absence of hormonal stimulation, mammary tumors were induced. The possibility exists that the irradiation may activate a weak milk factor but so far no such evidence has been obtained. In addition to mammary carcinomas, sarcomas at the site of the mammary gland were found in the

* Lorenz and Eschenbrenner, unpublished data.

irradiated LAF_1 and C_3Hb females. Their incidence was 33 per cent in the C_3Hb mice. They are called mammary sarcomas because mammary ducts are observable in the sarcomatous tissues. None of these tumors were observed either in the virgin controls or in the intensely bred animals. Such tumors do occur rarely, however, in other non-irradiated mice. These tumors are always associated with granulosa cell tumors of the ovaries in the irradiated animals. Whether these tumors are elicited by hormonal secretions of the ovarian tumors or by a direct action of irradiation on the mammary tissue cannot be decided at present.

As mentioned before, carcinogenic effects of long continued irradiation are also apparent in guinea pigs and rabbits. Because of the longer life span of guinea pigs in comparison to mice, many years are required to obtain sufficient data. In addition the severe effect of chronic irradiation upon the hematopoietic system of guinea pigs necessitates experiments in which the exposure is limited in time and total accumulated doses or to experiments at the dosage rate of 1.1 r per day. The data accumulated up to the present indicate an increase in incidence for lung tumors and mammary tumors in chronically irradiated animals of both sexes over that of nonirradiated controls.

4. Ovarian Tumors. While in the induction of the tumors discussed so far the dosage rate seems to be of greater importance than the total dose, the induction of ovarian tumors in mice is an exception. It is largely independent of dosage rate and depends on a minimum dose. Doses above this minimum dose merely shorten the tumor development time but have little influence on total incidence. The experimental data show that these tumors are the end product of a series of changes in the ovary starting with a depletion of follicles, followed by tubular downgrowth and resulting finally in tumor formation. The role irradiation plays in the genesis of these tumors seems to be to hasten only the first step, the depletion of follicles. The subsequent processes are not influenced by the irradiation. This is illustrated by the data of Table III. The tumor incidence shows considerable variations for comparable groups. This is due to the fact that in the various groups animals died of other diseases before they reached the ovarian tumor age. Nevertheless they show that the incidence is about the same whether the animals were exposed continuously on the 8.8 r level to a total dose of 3,500 r or whether at the same level the exposure was limited to a sterilizing total dose of 880 r or even smaller doses.

Table III

Incidence of ovarian tumors in LAF_1 mice

Experimental Group	No. of Animals	Incidence	Age When First Tumor Observed
		(per cent)	(months)
Controls	19	12	34
50 r (acute)	7	71	23
0.11 r	14	60	28
1.1 r	24	88	19
2.2 r	17	88	15
4.4 r	23	95	16
8.8 r	24	79	13
8.8 r (limited to 300 r)	8	100	17
8.8 r (limited to 600 r)	8	87	23
8.8 r (limited to 880 r)	16	63	13

The minimum dose necessary to induce ovarian tumors is quite small and is cumulative even at the dose rate of 0.11 r given in eight hours per day. In the control animals the ovarian tumor incidence was 12 per cent, whereas in the 0.11 r group the incidence rose to 70 per cent and the first tumors appeared earlier (Table III). The total dose accumulated at this level was approximately 90 r. It is also important to note that a single acute roentgen radiation dose of 50 r given in four and a half hours at the age of five months will result in an

TABLE IV

INCIDENCE OF CARCINOMA OF THE UTERUS IN RABBITS

Group	No. of Animals	Animals with Tumors	Animals with Metastasis	Mean Tumor Age	Age When First Tumor Was Found
				(months)	(months)
Control	6	2	None	57.5	57
0.11 r	3	None	—	—	—
1.1 r	3	3	2	52	49
2.2 r	3	3	2	56	50
4.4 r	3	3	1	41	35
8.8 r	3	2	2	36	33

incidence of 70 per cent. This dose seems to be the limiting roentgen radiation dose as animals exposed to 13 r of roentgen rays in four and a half hours showed no increased ovarian tumor incidence.

Apparently the ovarian tumors are induced by a local effect on the ovary. This is evidenced by the fact that comparable sterilization effects in mice are obtained when the animals are exposed to the same acute dose of roentgen radiation directed either to the ovary alone or to the whole body.* The possibility of a secondary endocrine contribution in ovarian tumorigenesis, as postulated by Li and Gardner,[12] is not yet excluded however.

5. Uterine Tumors. Late in life rabbits are known to develop a carcinoma of the uterus which is usually localized but metastasizes occasionally.[13] Two of 6 non-irradiated control animals were found to have localized tumors of this type while the majority of the irradiated animals developed this carcinoma, many of them at a considerably younger age (Table IV). Although the samples are smaller, incidence data observed in the 8.8 r to 1.1 r group are of high significance. It is interesting to note that the majority of the carcinomas of the irradiated animals showed extensive metastases to practically all organs, especially to the lungs, but metastases were not found in the control animals of this series. Recently Kaplan and Murphy[14] have shown that a transplanted mammary tumor in mice which does not metastasize ordinarily will metastasize when irradiated with doses insufficient to destroy the tumor. We may have to deal here with a similar phenomenon, the mechanism of which is obscure.

* Deringer and Lorenz, unpublished data.

SUMMARY

The data presented permit the following conclusions: Chronic irradiation will reduce the life span of experimental animals. This effect is a function of many factors some of which are unknown. The effects of irradiation are cumulative to a certain degree. Our experiments do not give a clearcut answer to the question whether or not a daily dose of 0.1 roentgen (the so-called "permissible" dose for man) also will cause a reduction in life span. Data on higher dosage rates make such a result likely but in any case the reduction at this dose level will be small. The determination of the extent of the reduction of life span for this important dose level requires the collection of experimental data on a large group of animals.

Carcinogenesis plays the most important role in the reduction of the life span in mice. The carcinogenic action of chronic irradiation has been observed in three species, one of which, the guinea pig, is considered one of the least susceptible animals to spontaneous tumor formation. It seems that we are justified in assuming that this carcinogenic action of chronic irradiation will hold for other species as well as for man. We are just beginning to acquire some information

as to the mechanism of tumor induction, or more specifically regarding the role which the endocrine system plays in radiation carcinogenesis of certain organs, but we are still a long way from understanding the fundamental process by which irradiation changes a normal cell into a cancer cell.

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CIRCULATION TIMES FOR ANGIOCARDIOGRAPHY

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THE use of a radiopaque substance for contrast roentgenographic visualization of the heart chambers and great vessels is a diagnostic procedure of increasing use and value. Recent advances in the surgery of congenital heart disease have brought preoperative angiocardiography into a position of diagnostic importance. The differential diagnosis of mediastinal masses and aneurysms is often materially aided by this procedure.[8] In some cases of this type, an angiocardiogram may be the only nonsurgical, absolute method of diagnosis available. The prevalence of these conditions renders it most desirable that a consistent method for satisfactory angiocardiography be widespread. Simplicity of method and absence of need for expensive or elaborate equipment are thus essential. Direct, rapid intravenous injection of an iodine compound such as diodrast as originally introduced by Castellanos[1] and by Robb and Steinberg[3] in 1938 is the method of greatest simplicity.

However, the diagnostic justification of the entire procedure frequently depends upon obtaining a roentgen exposure at the precise time the left heart and aorta are filled with dye. Failure to obtain a satisfactory levo-angiocardiogram robs the serial exposures of much of their value and exposes the patient to unnecessary discomfort. In the intravenous method this failure is discouragingly frequent. The injection of the contrast medium into the antecubital vein unavoidably subjects the rate of flow of the material to many variables. The caliber and length of the arm vein, the degree of its compression by the first rib influence the time for delivery of the dye to the right heart. Through the lung the rate of flow is variable and considerable dilution occurs there.

Advance determination of the precise instant when dye accumulates in the left heart and aorta in sufficient concentration for visualization has been difficult. The work on the procedure at Preble Laboratory in Cook County Hospital has suggested two modifications which greatly enhance the ability to obtain consistently levo-angiocardiograms with a minimum of exposures and equipment. The first of these is a test of patency of the individual's venous system from the antecubital vein to the right auricle; the second is a modified method to determine the circulation time.

In general, three methods have been previously employed in attempting to determine the exact timing of the roentgen exposures after the beginning of injection.

(1) In 1940 Robb and Steinberg[4] published the times they had found satisfactory for visualization, using the data gained from actual successful performances. However, as pointed out by Sussman, Steinberg and Grishman[6] such times are not invariably correct for levo-angiocardiograms.

(2) The determination of the circulation times of many substances has also been used as an additional aid in the spacing of the films. Ether arm to pulmonary capillary time and sodium cyanide arm to carotid times determined by the injection of from 2 to 20 cc. of various dilutions of these substances has been advocated.[3] These two materials give involuntary, objective end points and are thus held superior to numerous other compounds such as decholin, aminophylline and macosal,[9] which are

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This investigation was aided by the Department of Medical Research of Winthrop-Stearns, Inc., in furnishing the 70 per cent diodrast for the studies.
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subjective in response. Use of ether circulation times under such conditions has been adequate for dextro-cardiograms. However satisfactory right heart visualization is uniformly obtained two to three seconds after the beginning of the injection, if this is done under two seconds. Advance knowledge of the rate of injection possible is thus essential if a single exposure made at that time is to be adequate. But due to variation in pulmonary circulation, visualization of the left heart has still often remained a matter of chance.

(3) Increasing the total number and frequency of roentgen exposures taken has offered a partial solution to the problem. Numerous devices have been introduced to do this. Cameras of the 35 mm. film type have rapidly photographed a fluorescent screen with some loss of detail.[6] A rotary wheel cassette changer and other types have been devised. All such devices possess several faults. They demand an increased amount of physical apparatus, limiting the widespread use to which angiocardiography is entitled. Second, they all result in greatly increased roentgen-ray exposure of the patient and the team performing the technique.

TABLE I

EFFECT OF VOLUME ON ETHER AND SODIUM CYANIDE CIRCULATION TIMES

Patient	Circulation time in seconds				
	0.5 cc. ether dissolved in:		0.3 cc. 2 per cent NaCN dissolved in:		
	5 cc.	50 cc.	5 cc.	50 cc.	(saline)
E.A.	7.0	6.1	14.8	12.1	
J.B.	4.5	4.2	4.5	4.0	
J.A.B.	3.6	2.4	9.9	5.2	
W.S.	8.9	5.9	23.4	15.7	
A.S.	7.4	8.6	20.0	4.6	
L.D.	7.5	4.0	24.8	8.9	
C.C.	7.0	7.3	18.0	13.2	
F.M.	6.5	6.0	29.7	16.5	
A.T.	8.2	7.2	30.0	20.5	
L.G.	9.0	4.6	34.2	23.5	
S.L.	5.8	4.9	16.8	11.9	
C.L.	—	—	18.3	15.1	
M.M.	—	—	16.3	11.6	
L.H.	—	—	17.7	13.8	
H.A.	—	—	14.6	12.0	
W.L.	—	—	8.7	8.0	
A.Y.	—	—	24.5	18.6	
S.S.	—	—	16.9	12.9	
J.K.	—	—	29.4	19.1	
S.H.	—	—	15.6	15.5	
Mean	6.9	5.6	19.4	13.1	
Difference of means	1.3 seconds		6.3 seconds		

Previous work on circulation times has been extensive, but offered variable results. In 1945 Ruskin and Rockwell,[5] recognizing the great variations in reports on circulation time, studied the influence of dosage and volume on circulation time. They demonstrated that beyond an optimum effective dosage of any material (suitable for use in circulation times) further increase

caused no decrease in circulation time. Second, they pointed out that increasing the dosage over 5 cc. shortened the time enough to affect clinical measurements. Robb and Weiss,[2] in 1933, had demonstrated that 5 to 10 mg. or 0.35 cc. of a 2 per cent solution was the optimum dosage of NaCN. Confirmation of the effect of volume on circulation times is presented in Table I.

The difference between the mean sodium cyanide circulation time of the two volume groups is 6.3 seconds, and in every instance, the use of a 50 cc. quantity injected in two seconds or less gave a shortened circulation time.

Comparison of the decreases in circulation times resulting from the use of 50 cc. rather than 5 cc. quantities of solutions of ether and NaCN reveals the location and extent of the acceleration of passage of these solutions through the lesser circulation. Increase in the quantity of ether solution to 50 cc. resulted in a mean decrease in arm to lung capillary circulation time of 1.3 seconds. However a similar increase in quantity of NaCN solutions resulted in a decrease of arm to carotid time of 6.3 seconds. These figures imply that the use of the 50 cc. quantities hastens the passage of such a quantity through the lung by (6.3) minus (1.3) or 5.0 seconds. Such evidence would indicate that the pressure increase resulting from the rapid injection of the larger quantity of solution into the arm vein accelerates the rate of flow not only to the right heart, but through the lungs and left heart as well.

It was thus felt that the determination of the circulation times upon which angiocardiograms are to be based must be done in identical fashion to the actual injection of the dye. A difference in quantity of material, in site of or rapidity of injection, or position of the patient will alter the relationship. Accordingly, a group of patients, none of whom possessed heart valve deformities, were examined by angiocardiography preceded by multiple circulation time determinations. A large bore Lindemann needle was inserted by cut down procedure into an antecubital vein of each person. One-half cubic centimeter of ether dissolved in 5 cc. and in 50 cc. of saline, and 0.3 cc. of 2.1 per cent NaCN dissolved in 5 cc. and 50 cc. of saline were used in four separate circulation time determinations. The 50 cc. quantities were injected in a fashion, time, and quantity identical to the diodrast used shortly thereafter for visualization. The respective circulation times and their relation to the time at which the vessels and heart chambers were actually visualized is shown in Table II.

Successful levo-angiocardiograms were obtained almost uniformly by a roentgen exposure taken at a time differing not more than 10 per cent from the 50 cc. NaCN circulation time. In no case did this observed 10 per cent difference represent more than two seconds. Since this interval is shorter than the time for passage of an effective concentration of media through the left heart and aorta, these structures were, with but one exception, visualized in individuals without valvular heart disease by a single exposure taken within these narrow time limits. In addition, the use of such a method and quantity permits, in effect, a relatively harmless trial of the actual dye injection. No reactions were encountered in this method of determining circulation times, over and above the same response which smaller quantities give. Knowledge of the difficulty to be had in injecting 50 cc. of diodrast into each individual vein is learned beforehand and the risk of a slow and therefore ineffective injection of dye eliminated.

SUMMARY

(1) A method for the determination of circulation times prior to angiocardiography is presented.

(2) This method facilitates the accurate timing of exposures to be made in order to obtain levo-angiocardiograms. An effective decrease in number of serial exposures, and thus necessary equipment, and lessened radiation to the patient, is achieved.

TABLE II

RELATIONSHIP BETWEEN CIRCULATION TIMES OF ETHER AND SODIUM CYANIDE DISSOLVED IN 50 CC OF SALINE AND THE TIME FILMS TAKEN BY ANGIOCARDIOGRAPHY REVEALED DYE IN VARIOUS STRUCTURES

Patient	Circulation times with:		Time after beginning of injection at which films were taken and structures outlined in each film			
	Ether	NaCN	First	Second	Third	Fourth
E.A.	6.1	12.1	2 sec. SVC, RA, RV	5 sec. Pul. art.	8 sec. Pul. veins	12 sec. Complete aorta
J.B.	4.2	4.0	2 sec. RA, RV, Pul. aorta	6 sec. LV, Aorta	9 sec. Aortic knob	12 sec. No dye
J.A.B.	2.4	5.2	2 sec. RV, Pul. arteries	5 sec. Pul. veins Aorta	8 sec. LV. and aorta	12 sec. No dye
W.S.	5.9	15.7	3 sec. RV, Pul. arteries	8 sec. Pul. veins LV	11 sec. LV, aorta	14 sec. Aorta
A.S.	8.6	4.6	1 sec. SVC	3 sec. RV, Pul. arteries	5 sec. Lung	No film
L.D.	4.0	8.9	2 sec. RV, Pul. arteries	6 sec. Lung	8 sec. LA, LV	10 sec. LV, aorta
C.C.	7.3	13.2	2 sec. RV, Pul. arteries	5 sec. Pul. arteries	8 sec. Lung, Aorta (?)	12 sec. Aorta
F.M.	6.0	16.5	2 sec. SVC, RA	5 sec. RV, Pul. aorta	9 sec. Lung	16 sec. Lv, Aorta
A.T.	7.2	20.5	2 sec. SVC, RA	8 sec. Lung	11 sec. Lung	18 sec. Aorta
L.G.	4.6	23.5	3 sec. RV, Pul. arteries	9 sec. Lv, Aorta (?)	12 sec. Aorta	15 sec. Aorta
S.L.	4.9	11.9	3 sec. SVC, RA, RV	5 sec. RV, Pul. arteries	10 sec. LV, aorta	No film

SVC: superior vena cava; RA: right auricle; RV: right ventricle; Pul. aorta: pulmonary aorta; Pul. arteries: pulmonary arteries; Pul. veins: pulmonary veins; LV: left ventricle.

(3) The acceleration of circulation times observed with the use of 50 cc. quantities is attributed not only to increased rate of passage through the arm veins to the heart, but also to the increase in rate of flow of the material through the right heart, lung capillaries and left heart.

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PULMONARY COMPLICATIONS OF INSULIN SHOCK THERAPY*†

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LYONS, NEW JERSEY

INSULIN coma therapy is an established method of treating certain mental disorders, particularly schizophrenia. It has been used extensively in this country for about ten years, but published reports on its complications have been few in number. Pulmonary complications, although not uncommon, have received little attention in roentgenological literature and it is felt that roentgenologists, especially those associated either with hospitals or with physicians treating mental disease, should be familiar with these complications. This paper reports 3 cases of such complications encountered over a one year period at the Veterans Hospital, Lyons, New Jersey, as illustrative of the problem.

Since the initial report of the use of insulin in shock therapy by Sakel[9] several reports have appeared in which a variety of pulmonary complications were mentioned including bacterial and aspiration pneumonia, lung abscess, patchy atelectasis, pulmonary edema, congestion due to cardiac decompensation, pulmonary embolism and activation of quiescent tuberculous infiltrations. In an analysis of 90 deaths due to insulin shock therapy, Kinsey[6] attributed 22 to pulmonary complications. Nine of these were ascribed to aspiration pneumonia, 7 to other pneumonia, 3 to lung abscess, 1 to tuberculosis, and 2 to miscellaneous causes. Gottesfeld[3] noted that 1.1 per cent of his 272 cases developed pulmonary edema. Nielsen[7] observed three episodes of pulmonary edema during 1,200 insulin comas. In "over 100" cases O'Neill[8] had 4 cases of pneumonia and 2 cases of lung abscess.

TECHNIQUE[5]

The danger of pulmonary complications is inherent in the technique of insulin shock therapy. Five times weekly regular insulin is injected in amounts which will cause in the patient first a "pre-shock," or precomatose, state and later a "shock," or comatose state. During these stages, restlessness, hyperactivity, thrashing about and excessive salivation are common and occasionally there is laryngeal spasm. The comatose stage is allowed to exist for about an hour and is terminated by the administration of glucose, either orally, intravenously, or in combination. Patients are observed carefully and if signs of respiratory distress are noted appropriate emergency treatment such as oxygen, aspiration, respiratory stimulants, etc., are rendered. Persistence of symptoms calls for a complete diagnostic procedure. The interpretation of roentgenograms of the chest is facilitated by comparison with the "pre-shock" film taken before any treatment is given, as is customary in most hospitals.

During a one year period, 1,650 insulin treatments were given to 87 patients at the Lyons Veterans Hospital. Below are described three acute pulmonary complications encountered during the year. Inasmuch as pneumonia following insulin coma cannot be conclusively correlated with the course of therapy, cases of this type are not included in this report.

CASE REPORTS

CASE 1. B. D., a white male, aged thirty-two, was admitted to the Lyons Veterans Hospital with the diagnosis of schizophrenia, hebe-

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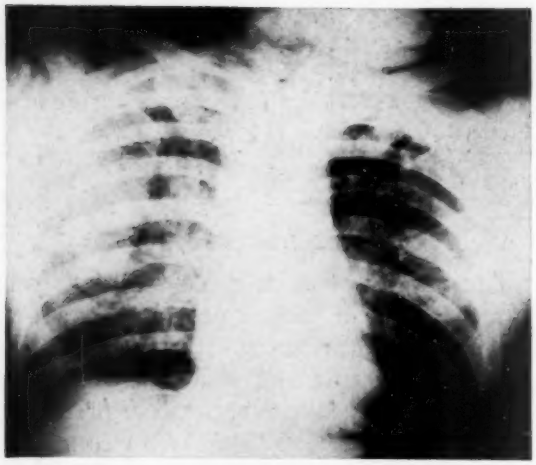

FIG. 1. Case I. Disseminated patches of pulmonary infiltration one hour following respiratory distress.

phrenic type. Physical examination and chest roentgenogram were completely negative, as were routine serological examinations and other laboratory findings. The patient was given two courses of electroshock therapy without incident. Insulin shock therapy was started during the first two weeks. Coma had to be terminated early twice because of respiratory embarrassment. During the fifth week the patient suddenly became apneic and cyanotic while the coma was being terminated with intravenous glucose. His blood pressure fell to 80/0 and his pulse rate dropped to 60; his temperature rose to 103° F. Rales were heard at both bases. Treatment consisted of oxygen, respiratory stimulants, and aspiration. After several hours, the patient regained full consciousness and coughed profusely. Both penicillin and digitalis therapy were initiated. A chest roentgenogram (Fig. 1) taken about an hour after the initial episode showed disseminated patches of clouding scattered throughout both lung fields, but the heart shadow appeared normal. The roentgenological diagnosis was disseminated bronchopneumonia and the possibility of pulmonary edema was suggested. The electrocardiogram showed changes slightly suggestive of myocardial damage. Within the next forty-eight hours the patient improved rapidly, the temperature fell to normal, rales were decreased and the electrocardiogram reverted to normal. The chest film (Fig. 2) also showed almost complete resolution of the previously reported findings and the patient was considered recovered.

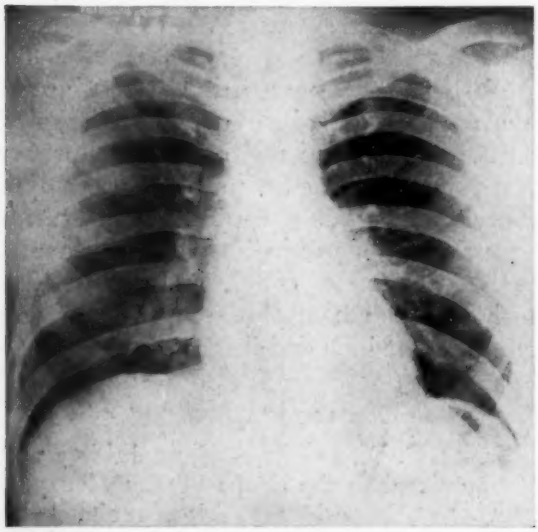

FIG. 2. Case I. Roentgenogram taken twenty-four hours later showing complete resolution of the pulmonary infiltrations.

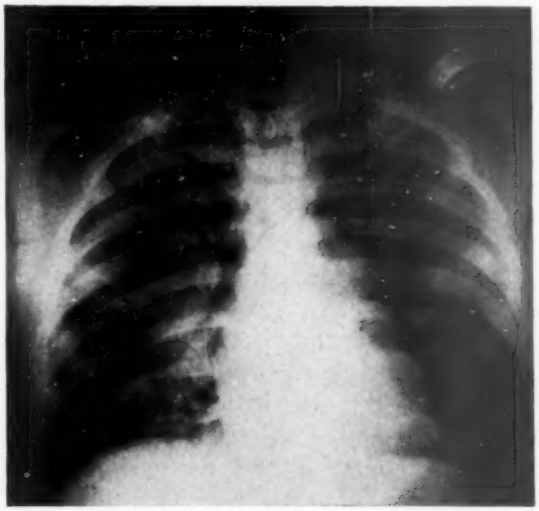

FIG. 3. Case II. Widely disseminated patches of infiltration and congestion in both lung fields.

CASE II. L. M. C., a white male, aged twenty-three, was admitted to the Lyons Veterans Hospital with the diagnosis of schizophrenia. Physical examination was completely negative as was the chest roentgenogram. The electrocardiogram showed some evidence of myocardial damage. Insulin therapy was initiated and was uneventful until the seventeenth

treatment. While coma was being terminated by gavage with glucose solution, the patient became cyanotic and vomited blood tinged material. Respirations were shallow but the pulse was regular and full. Temperature rose to 106° F. Supportive therapy including oxygen was given as well as digitalis and penicillin. Bronchoscopy revealed inflamed mucous membranes and a moderate amount of purulent secretion which was aspirated. Coughing occurred to some extent. Roentgenogram of the chest (Fig. 3) showed widely disseminated patchy areas of pneumonic infiltration scattered throughout both lung fields and especially in both hilar regions. The heart shadow appeared

Fig. 4. Case II. Roentgenogram taken three days following respiratory episode showing complete resolution.

normal. Among the diagnoses considered were aspiration pneumonia and pulmonary edema. The following day the temperature began to fall and the patient appeared improved, but the roentgenogram showed essentially the same findings. Bronchoscopy was repeated and a moderate amount of purulent material aspirated. On the third day the roentgenogram (Fig. 4) was clear and on the fourth day the temperature was normal, and the patient was well except for a cough.

Case III. J. P., a white male, aged twenty-four, was admitted with a diagnosis of schizophrenia. Physical examination and laboratory findings were negative, as were the chest roentgenograms and electrocardiogram. During the twenty-ninth insulin treatment, it was noted

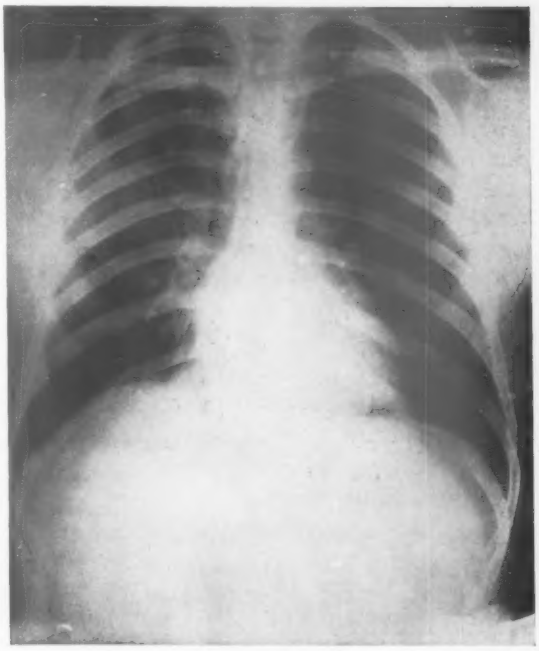

Fig. 5. Case III. Irregular consolidation of the right upper lung field.

that the patient was cyanotic and that his pulse was imperceptible. Rales were heard at the bases. A chest film (Fig. 5) showed irregular consolidation of the right upper lobe radiating from the right hilum to the level of the second and third interspaces anteriorly. He was treated with respiratory stimulants and intravenous glucose. He complained of a full sensation sub-

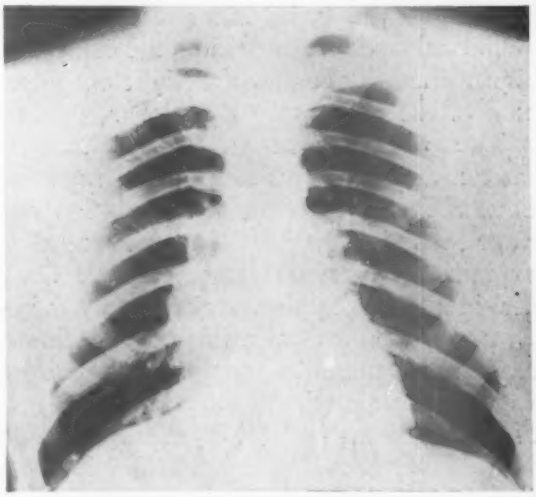

Fig. 6. Case III. Roentgenogram taken twenty-four hours after episode showing complete resolution.

sternally and then coughed up about 2 ounces of bright red blood. Temperature was 104° F., but fell to normal within twenty-four hours. A chest roentgenogram (Fig. 6) taken twenty-four hours after the episode showed complete resolution of the infiltration. An electrocardiogram made two days after the episode revealed evidence of myocardial damage, but this was repeated three days later and showed almost complete regression of these changes. The patient was essentially recovered at this time.

DISCUSSION

Case I and Case II appear to have been episodes caused by pulmonary edema, perhaps secondary to cardiac embarrassment. The results of the bronchoscopy in the second case would indicate that aspiration also played a role. Case III was at first thought to be due to a pulmonary infarct, but the rapid clinical and roentgenological reversion to normal made atelectasis the more likely diagnosis. All 3 cases were characterized by rapid resolution of the pulmonary pathologic process as shown by the serial roentgenograms. It was felt that perhaps pulmonary changes detectable by roentgenography occurred frequently in the post-shock patients, but that these were missed because the patients were asymptomatic. To put this theory to test, 18 unselected cases were roentgenographed immediately after the termination of coma. None of these cases showed evidence of pulmonary edema or pneumonic consolidation although one showed slight exaggeration of the pulmonary markings.

The pathogenesis of the pulmonary complications of insulin shock therapy has been the subject of much speculation and numerous theories have been advanced to explain the various complications. Gralnick[4] found that pulmonary edema was not an uncommon complication and mentioned among the possible causes: (*a*) a central nervous system effect due to hypoglycemia of the medulla; and (*b*) hyperadrenalemia causing left heart failure. Farber[2] induced pulmonary edema in rabbits experimentally by producing laryngeal paralysis and vagal nerve paralysis. Gottesfeld[3] believed that hypoglycemia interfered with the physicochemical phenomenon of muscle contraction of the heart muscle itself and that this was the forerunner of pulmonary edema. Allergy has also been suggested as an important factor in pulmonary edema. Altschule and Tillotson[1] reported a mechanism whereby aspiration occurs during the maximal inspiration at the termination of a convulsion. Although they were referring to electroshock, convulsions occasionally do occur during insulin shock. Whatever the mechanism, it seems certain that atelectasis, pneumonitis, and lung abscess are due to the aspiration of saliva, mucous, or gastric contents during some stage of the insulin treatment.

From the nature of the pulmonary complications, a single cause for all would not be expected. Clinical and experimental studies lead to the conclusion that the three major factors thus far uncovered which, either alone or in combination, cause pulmonary complications are: (*a*) aspiration of infectious material; (*b*) direct or indirect interference with cardiac function, and (*c*) interference with the function of the pulmonary and cardiac centers in the medulla. The role of allergy requires further investigation.

SUMMARY

1. Three cases of pulmonary complications of insulin shock therapy, in which serial roentgenograms were taken, are reported.

2. The pathogenesis of the various types of pulmonary complications is discussed.

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THE ROENTGEN APPEARANCE OF THYROID METASTASES IN BONE*

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INTRODUCTION

THERE are a few cancer metastases in bone that present a sufficiently unusual appearance in the roentgenogram to make possible an accurate appraisal of their origin. Perhaps the best example is prostatic cancer. A recent study[8] indicates that some metastases from cancer of the kidney present distinguishing characteristics. Articles on thyroid cancer note the incidence and location of metastases in bone, but no complete analysis of the roentgen features is presented.[1–7,10] Although Turner and Jaffe,[9] on the basis of their experience, stated that metastases from cancer of the thyroid were almost without exception osteolytic, they did not evaluate other roentgenographic features. Since there has been no complete discussion of the roentgenographic findings in a series of cases of thyroid cancer in bone, we were prompted to study the material at Memorial Hospital to determine if there was any specificity.

Four hundred and thirty-four cases filed as thyroid cancer were available. There were 35 of these with metastases in bone that had adequate roentgenograms available. The Department of Pathology classified these 35 cases as follows: solid and small alveolar carcinoma, 1; pleomorphic alveolar adenocarcinoma, 1; embryonal adenocarcinoma, 1; papillary and solid adenocarcinoma, 1; solid adenocarcinoma, 1; solid and papillary carcinoma, 1; metastasizing struma and alveolar adenocarcinoma, 1; papillary spindle and giant cell carcinoma, 1; unclassified carcinoma, 1; spindle cell carcinoma, 2; follicular and alveolar adenocarcinoma, 3; Hürthle cell carcinoma, 3; metastasizing struma, 3; adenocarcinoma, 5; alveolar adenocarcinoma, 5; papillary adenocarcinoma, 5.

Every case had at least one pathological report consistent with thyroid origin. These reports were based either on tissue from the primary lesion or from the metastasis, or in a few instances from both. The pathological diagnosis might have been based upon tissue from surgical specimen or biopsy, aspiration biopsy, or postmortem examination. If biopsy material from a metastasis were reported as cancer indicative of thyroid origin and if in addition there was clinical evidence of a mass in the thyroid, the case was accepted. Similarly, if a thyroid cancer was removed and metastases were subsequently revealed in bone, the case was included.

There were 22 males and 13 females with ages ranging from thirty-three to seventy-four years. Thirteen of these patients had had their thyroid cancer removed previously. In these the time interval between the thyroidectomy and the demonstration of the metastases in bone varied from nine months to nine years, with an average of about four years. Eleven of the 35 patients are living. Two have had metastases in bone for 7.7 and 9.5 years. In the 11 living patients the average time of survival from the discovery of the bone involvement was 3.3 years. In the 24 who have died the survival time after the appearance of the metastases extended from three months to eight years, the average being nearly three years.

The disease in bone was responsible for the initial visit to the physician in 19 instances. Pain was the chief complaint of 14 patients. A localized swelling was found in 19 individuals and 7 of them had pulsating

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tumors. Two of the pulsating tumors had a bruit and 3 of the 4 lesions that occurred in the sternum were of the pulsating type.

It seemed that roentgen therapy to the metastases resulted in relief of pain only occasionally. In a few instances a soft tissue mass became smaller. The few cases that showed clinical improvement with radioactive iodine revealed continued growth of the metastases in the roentgenograms.

ROENTGEN APPEARANCE

This study of thyroid cancer metastases in bone is based primarily on the earliest roentgenograms. If further roentgenograms were available, the effects of growth and treatment were appraised. In those cases having multiple involvement, it did not seem necessary to describe each bone lesion. Therefore, the largest or most representative was selected. Had there been a significant discrepancy between the metastases in any one case, we were prepared to make note of it. However, except in a few instances where a bulky metastasis which showed a little productive change was associated with multiple small, purely osteolytic lesions, there was a general constancy in appearance.

Location in the Skeleton. It was determined from a study of all the roentgenograms available on the 35 cases that there were 18 patients in which more than one bone was involved and 17 in which the disease was in one bone. The distribution of all the lesions detected by roentgen examination according to area involved was as follows:

Spine	18	Femur	5
Pelvis	13	Sternum	4
Ribs	12	Humerus	3
Skull	8	Scapula	2

Site of Origin. There were 34 cases where the origin seemed to be medullary and 1 where the cortex might have been the point of inception.

Pathological Fracture. There were 5 fractures in this series as revealed by a study of the earliest roentgenograms. There were a few additional fractures noted on subsequent films.

Size. Because most of the tumors selected for study were circular or oval in configuration, size was judged by measurement of the diameter. Those lesions having a diameter 5 cm. or less were called small, those over 5 and under 10 cm. were designated as medium, and those 10 cm. or over as large. Upon this basis the 35 tumors were grouped as follows: small, 17; medium, 10; large, 8.

Shape. The periosseous as well as the osseous part of the metastasis was included in a judgment of tumor shape. There were 26 tumors that were oval, 6 circular, and 1 was of a saucerized configuration. In 2 instances the shape could not be dependably evaluated.

Symmetry. This concept applies to the tubular bones and denotes whether or not the axis of a tumor coincides with the long axis of the shaft. In 12 cases where it was applicable, 7 tumors were found to be symmetrical and 5 asymmetrical.

Borders. An evaluation of the sharpness of the margins of these tumors was attempted. There were 22 with indistinct borders, 7 with distinct edges and 6 with distinct areas in the otherwise ill defined periphery.

Periosteum. There was no periosteal reaction found in any tumor.

Cortex. There were 3 instances in which the condition of the cortex could not be dependably evaluated. In the remaining 32 there were varying amounts of destruction, usually irregular in form. There was no cortical expansion, but thinning, a form of destruction, was common.

Destruction of Medullary Bone. Every tumor in this series showed medullary bone destruction. In 19 the destruction was pure and complete, being unaccompanied by any attempt at the formation of new bone, osteoid material or calcification. In the remaining 16 there were very slight productive changes, but in no instance did they approach the degree of destruction.

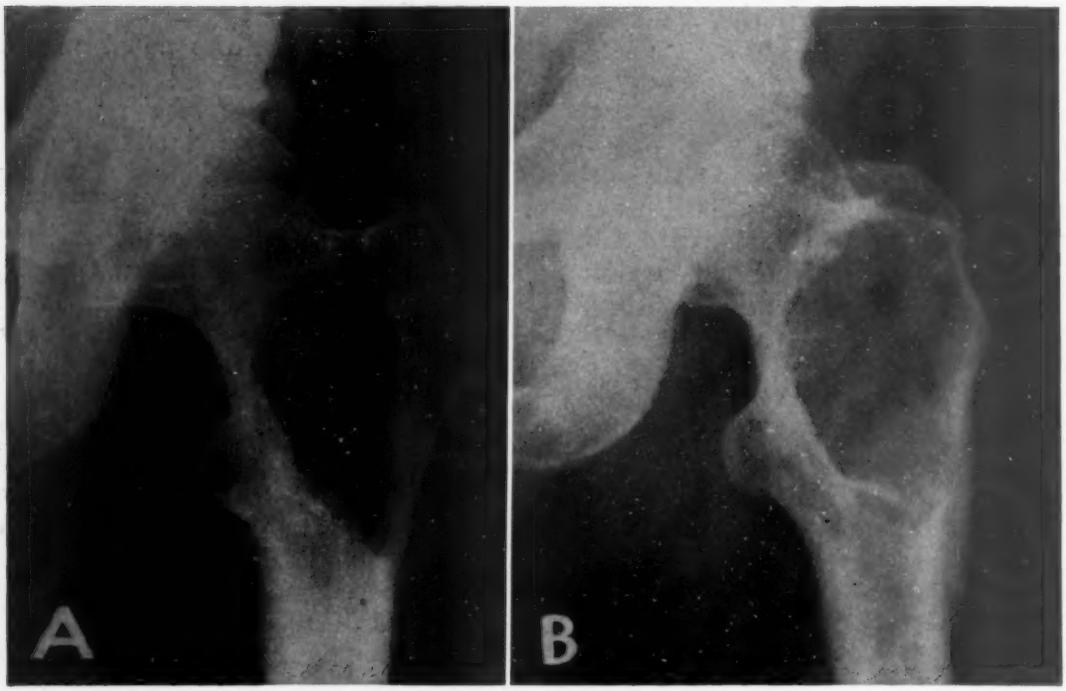

Fig. 1. (*A*) An osteolytic type of metastasis, having no internal pattern. (*B*) Appearance more than two years later and after 3,600 r (air). Borders are denser and sharper.

Fig. 2. An unusually well delineated septate type metastasis.

Soft Parts Extension. There were 21 lesions that were associated with extension into the periosseous structures. These extensions were graded as small, medium and large, the basis of comparison being the size of the medullary area of bone involvement. There were 7 in which the soft parts mass was small, 9 in which it was medium, and 5 in which it was large.

Direction of Growth. An attempt was made to ascertain whether the tumor tended to extend within bone or to break through the cortex and grow into the enveloping structures. In 24 there seemed to be about equal amounts of growth within and outside of the bone, whereas there were 8 in which the growth was located within bone, and 3 in which extension seemed to be largely beyond bone.

Internal Pattern. In this series there were 19 tumors that had no internal pattern (Fig. 1*A* and 4). Among the remaining 16 there were 5 metastases showing septation.

The septa were somewhat irregular and frequently were incomplete, but they tended to form small oval loculations. Four of the 5 lesions of this type occurred in the pelvis (Fig. 2 and 5). In the other 11 lesions that showed productive change such formation was confined to a few scattered amorphous calcific flecks or meagre and quite incomplete septa (Fig. 3, 6, 7 and 8). Included in this group of 11 are several that showed only a marginal increase in density in certain segments of the border.

Destruction in Continuity. There were 6 tumors in which destruction beginning in one bone apparently crossed over a joint and extended into other bones. Favorite sites for this rather unusual type of growth were the spine and ribs (Fig. 4), pelvis and hip (Fig. 5) and ilium and sacrum (Fig. 6). In 1 case observation over a period of time

Fig. 4. Destruction in continuity between vertebrae and rib.

Fig. 3. (*A*) An osteolytic lesion with scattered amorphous calcification. (*B*) Appearance six months after 2,500 r (air) to each of three fields. The tumor is denser and its borders are sharper.

FIG. 5. A septate type of metastasis extending by destruction in continuity into the head of the femur.

showed the actual progression across a joint from one bone into another.

Growth Effects. There were 5 cases in which metastases were followed over a sufficiently long period by roentgenograms so that something about the growth rate could be determined. One small tumor that was untreated for nearly three years increased about six times in size during this time. Its essential appearance did not change. A tumor in the pelvis that was followed for one year grew from 5 to 6 cm .in diameter and seemed to deposit a few calcific flecks. A metastasis in a rib nearly doubled its size in four months, while one in the spine and one in a rib seemed unchanged over a three months' period of observation.

Treatment Effect. There were 20 cases where sufficient time had elapsed after roentgen treatment to permit some evaluation of its effect roentgenographically. Some of these tumors were followed for several years. A judgment as to the type and amount of treatment was of course necessary in studying the effect in the roentgenogram.

The changes related to roentgen treatment were the formation of strands, calcific deposits, and a dense border. In addition, several tumors seemed to show merely an absence of growth. A few continued to enlarge as though unaffected by irradiation. Two which became a little larger in spite of treatment also showed the formation of a few calcific deposits. In no instance did the fundamental nature of the metastasis change (Fig. 1*A*, 1*B*, 3*A*, 3*B*, 7*A*, 7*B*, 8*A*, 8*B* and 8*C*).

Metastases in Chest. Most of the 35 patients had chest roentgenograms available. There were 13 patients in whom metastases were noted in the roentgenogram of the chest at some time during the course of the disease. These metastases were usually small scattered nodules. Secondary deposits were also occasionally seen in the mediastinal and hilar areas.

Pulsation. There were 7 tumors that

FIG. 6. Destruction across the sacroiliac joint presumably by continuity. This is an osteolytic type of metastasis with productive strands, calcific flecks and dense segments in the border.

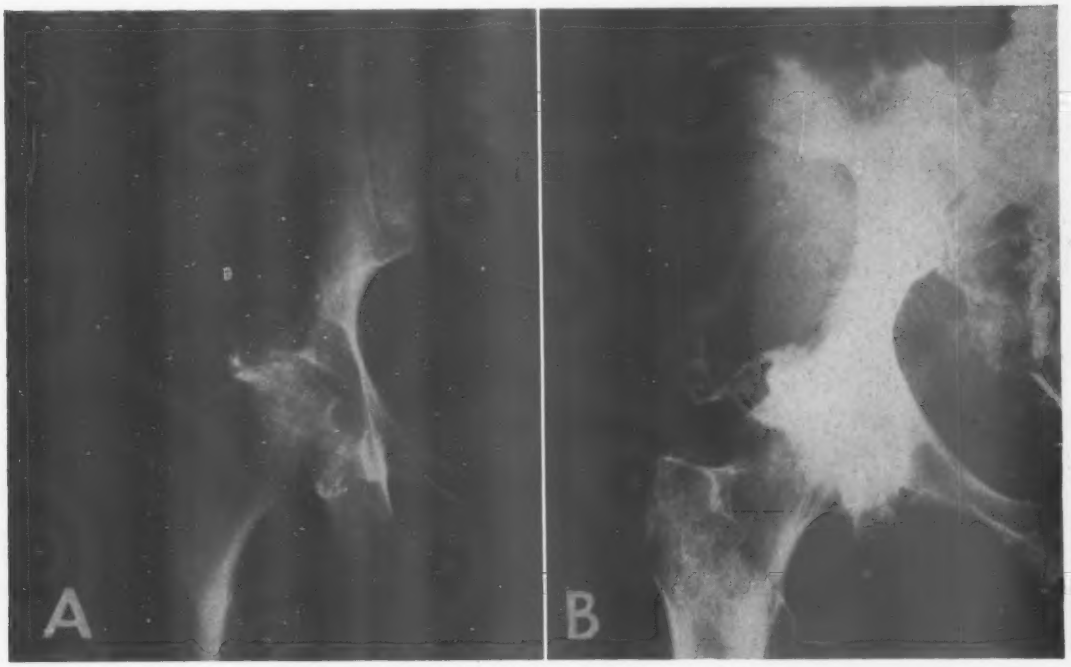

Fig. 7. (*A*) A lytic type of metastasis showing a few calcific strands. (*B*) The appearance almost three years later following 2,100 r (air) to three fields. The soft parts mass is smaller, borders are denser. The untreated lesion in the ischium is larger.

pulsated. The distribution was as follows: sternum 3, ilium 3, rib 1. There seemed to be nothing characteristic in the roentgen appearance to indicate that they were pulsating lesions.

Summary of Roentgen Appearance. Thyroid cancer metastasis in bone as seen roentgenologically presents constant features of medullary origin, medullary and cortical bone destruction, and absence of periosteal reaction. In addition, there is almost always an oval shape, small to medium size, small to medium soft parts extension, indistinct borders and an essentially osteolytic internal pattern. If present at all, production takes the form of faint septa, calcific flecks and small dense areas at the borders. A somewhat unusual feature that is occasionally seen is destruction in continuity. The metastases seem to be relatively radioresistant as judged by roentgenographic studies, the slight productive changes formed occasionally not basically altering the roentgen appearance.

In our material there was a single case that did not satisfactorily conform in roentgen appearance to the other metastases but which for completeness we feel should be included. This patient was a female, aged fifty-seven, with a presenting symptom of hemoptysis. She had first noted weakness for several months and then developed a cough with blood-streaked sputum for several weeks prior to admission. A roentgenogram of the chest showed a rounded mass in the right mid-lung field 4 cm. in diameter and metastatic disease in the left second rib. A diagnosis of bronchogenic carcinoma with metastasis to bone was made roentgenographically. Sputum studies and bronchoscopy were negative. A biopsy of the rib was reported as metastatic carcinoma, not bronchogenic. This led to a search for the primary lesion, during which a 1.5 cm. nodule was found in the right lobe of the thyroid. This was biopsied and reported as Hürthle cell carcinoma of the thyroid. The rib metastasis was thought to be consistent histopathologically with this primary lesion. Metastasis later developed in the

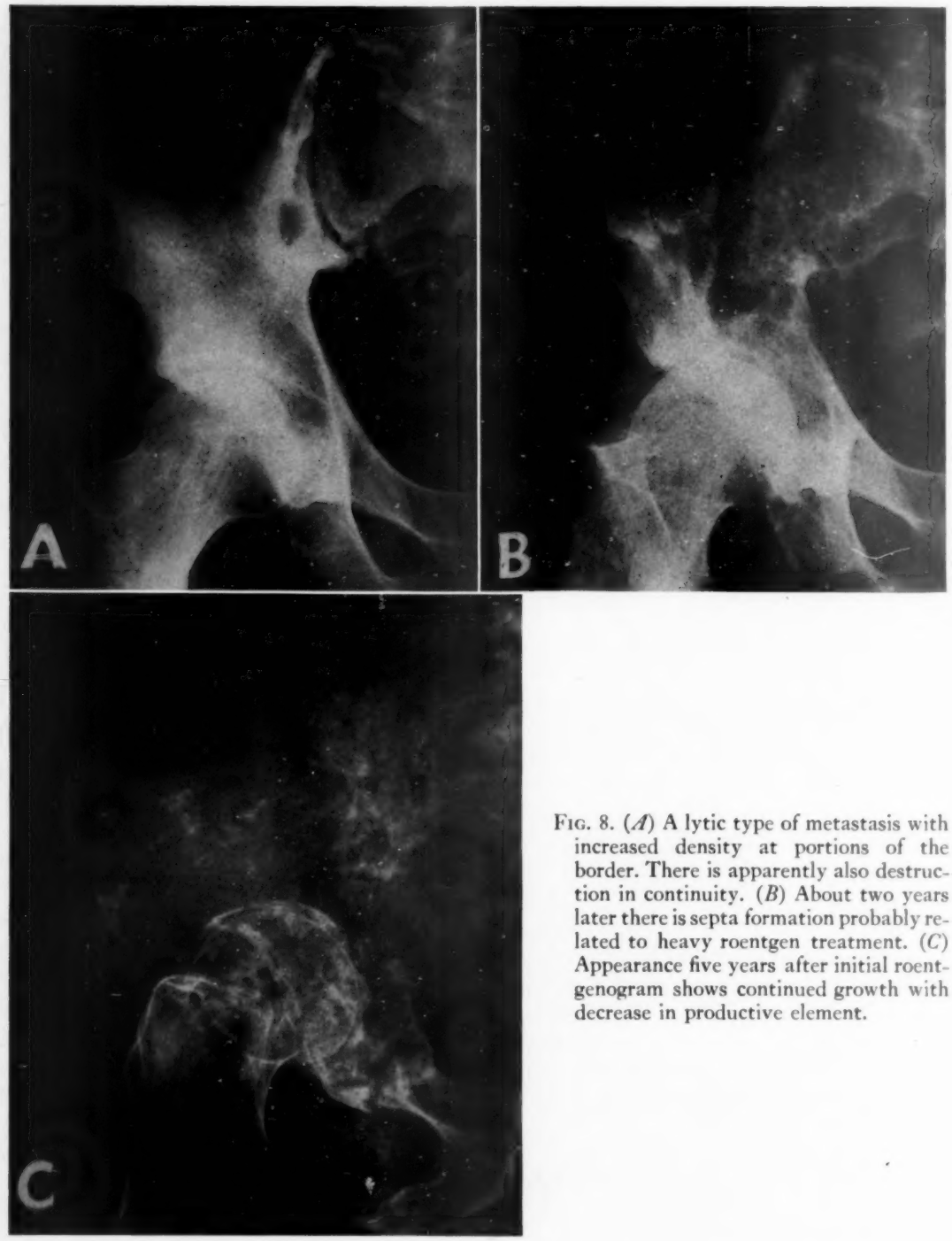

FIG. 8. (*A*) A lytic type of metastasis with increased density at portions of the border. There is apparently also destruction in continuity. (*B*) About two years later there is septa formation probably related to heavy roentgen treatment. (*C*) Appearance five years after initial roentgenogram shows continued growth with decrease in productive element.

pelvis. The patient died one and one-half years following the onset of symptoms. No autopsy was obtained. The roentgen appearance of both the rib and pelvic lesions was that of a predominantly osteoblastic metastasis. In view of the appearance of the metastases, the presence of a large solitary lesion in the lung and the presenting symptom of hemoptysis, this case was considered to be atypical for thyroid cancer metastasis.

DIFFERENTIAL DIAGNOSIS

There were 5 tumors that approached a septate pattern. In general, this septation was of an incomplete degree. The septa were fine, delicate and often sketchy. The loculation was less developed than that expected in either giant cell tumor, adamantinoma, septate form of kidney cancer metastases or certain myelomas. It seems that the differential diagnosis for these 5 cases beyond their recognition as metastases would be concerned with distinguishing them from osteolytic osteogenic sarcoma, certain forms of metastases from cancer of the kidney or "solitary" myelomas. The fineness and incompleteness of the septa, destruction in continuity if present, and absence of periosteal reaction might be the features pointing to thyroid origin, but in most instances an absolute differential diagnosis probably could not be made in this group.

There were 11 tumors which revealed a few strands or calcific flecks. These 11 cases along with the remaining 19 purely osteolytic ones are indistinguishable from any other metastasis of osteolytic type. Osteolytic osteogenic sarcoma, certain forms of myeloma, and such osteolytic processes as eosinophilic granuloma and lymphoid involvement might tend to appear similar. When present, destruction in continuity might be a clue to thyroid origin. One point of significance in differential diagnosis, however, is that any lesion having the roentgen characteristics of a metastasis and having an equal or greater degree of production as compared with destruction is probably not of thyroid origin.

SUMMARY

1. Thirty-five proved cases of thyroid cancer metastases in bone are studied from the standpoint of roentgen diagnosis.

2. The salient roentgen features of this type of tumor are listed and a basically uniform roentgen appearance is noted.

3. A somewhat unusual feature, bone destruction in continuity, is described.

4. To be of thyroid origin, a metastasis should be either predominantly or purely osteolytic.

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A PNEUMOENCEPHALOGRAPHIC STUDY OF THE NORMAL THIRD AND FOURTH CEREBRAL VENTRICLES AND AQUEDUCT OF SYLVIUS*

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ONE of the essentials in pneumoencephalographic examination is the identification of the third ventricle, the aqueduct of Sylvius and the fourth ventricle. At present most information available is related to their configurations and positions.[1,5] There are few data as to their relative sizes, the most complete being that reported by Dyke and Davidoff.[2] In order to obtain further and somewhat more detailed information concerning the sizes as well as the shapes of these midline cerebrospinal fluid passages, 50 normal pneumoencephalograms in which the visualization was adequate for measurement of these chambers were reviewed. Both lumbar pneumoencephalograms and ventriculograms were included in this series. In 23 cases, midline laminagrams were available. By the elimination of superimposed gas and bone shadows the third ventricle, aqueduct and fourth ventricle could be more sharply delineated than on the routine roentgenograms.[4]

VARIATIONS IN THE CONTOUR OF NORMAL THIRD VENTRICLES

In the lateral projection the third ventricle is somewhat trapezoidal in configuration. Its anterior wall slopes from above downward and anteriorly, so that its anteroinferior angle is approximately 45 to 60 degrees. This angle may be relatively sharp or somewhat rounded. The length of the anterior wall varies from 2.3 to 3.1 cm. The uppermost limit is the inferior lip of the foramen of Monro. Immediately beneath is a slight indentation which is quite difficult to demonstrate pneumoencephalographically, but which may occasionally be seen as a small white dot corresponding to the anterior commissure. The lamina terminalis makes up the remainder of the anterior wall, which is straight or somewhat convex outward. Less frequently a very slight concavity may be seen. To either side of the lamina terminalis, in the junction of the anterior and lateral walls, lie the anterior pillars of the fornix, which cannot be demonstrated specifically on the roentgenograms.

The floor of the third ventricle is variable in configuration. It may extend directly caudad as a relatively straight line inclined slightly upward, or the floor posteriorly may be represented by a curvilinear upward convexity. If the degree of filling is poor, or if the walls of the third ventricle are close together, this apparent indentation may be exaggerated. It should not be confused with a mass protruding into the posteroinferior aspect of the third ventricle. The floor, from before backward, is formed by the optic chiasm, the infundibulum, the tuber cinereum, the mammillary bodies, the posterior perforated space, the cerebral peduncles and the tegmentum of the midbrain. At the anteroinferior angle lie the chiasmal and infundibular recesses, which may be quite difficult to demonstrate.

The posterior wall of the third ventricle begins at the aditus of the sylvian aqueduct inferiorly. Immediately above this and sloping slightly dorsally are the posterior commissure, the pineal recess and the suprapineal recess. The suprapineal recess is considerably larger than the pineal recess, and may measure up to or slightly over 1 centimeter in length.

The roof of the third ventricle is formed by the velum interpositum stretched between the thalami, beneath which are sus-

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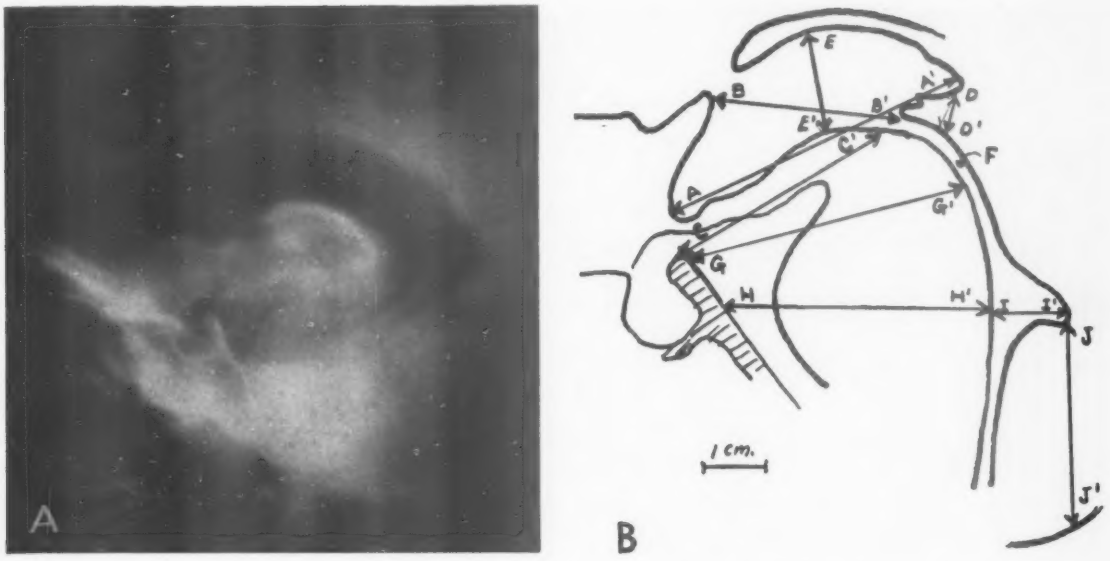

FIG. 1, *A* and *B*. Normal third ventricle, aqueduct of Sylvius and fourth ventricle. Midline laminagram and line drawing to scale. See Table 1.

pended the choroid plexuses covered by ependymal lining. When the third ventricle is completely filled with gas, the roof may be demonstrated as a curvilinear structure convex upward and sloping from before backward following the sweep of the fornix. If the upper aspects of its walls are closely apposed in the posterior half of the chamber the entrance of gas may be impeded. When this occurs the anatomic roof of the third ventricle cannot be seen, and a relative downward convexity which seems to protrude into its cavity appears. This must not be mistaken for organic pathologic change. When the suprapineal recess is not seen, care should be exercised in passing on

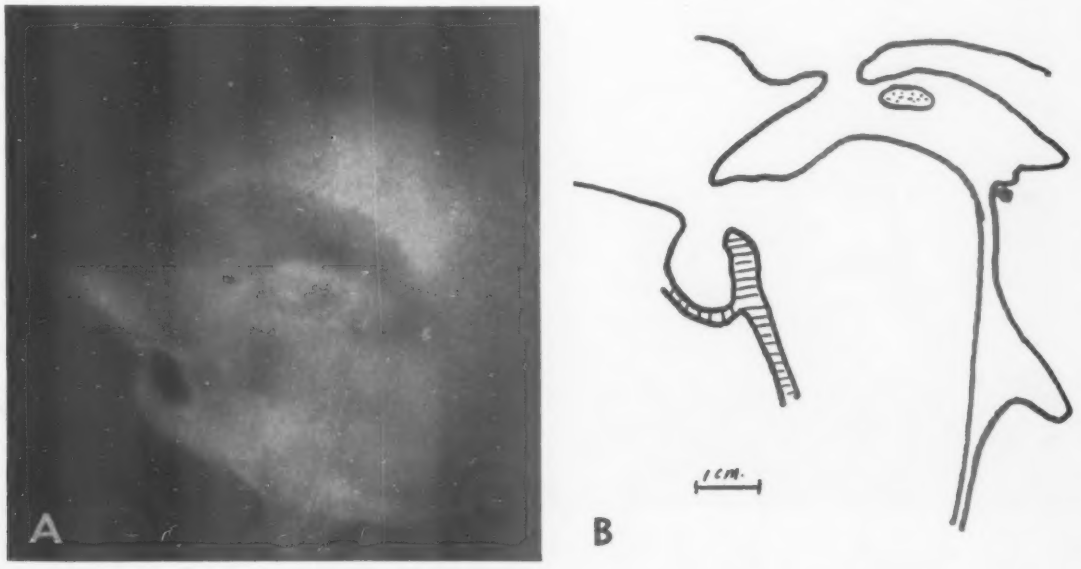

FIG. 2, *A* and *B*. Normal third ventricle, aqueduct of Sylvius and fourth ventricle. Midline laminagram and scale line drawing.

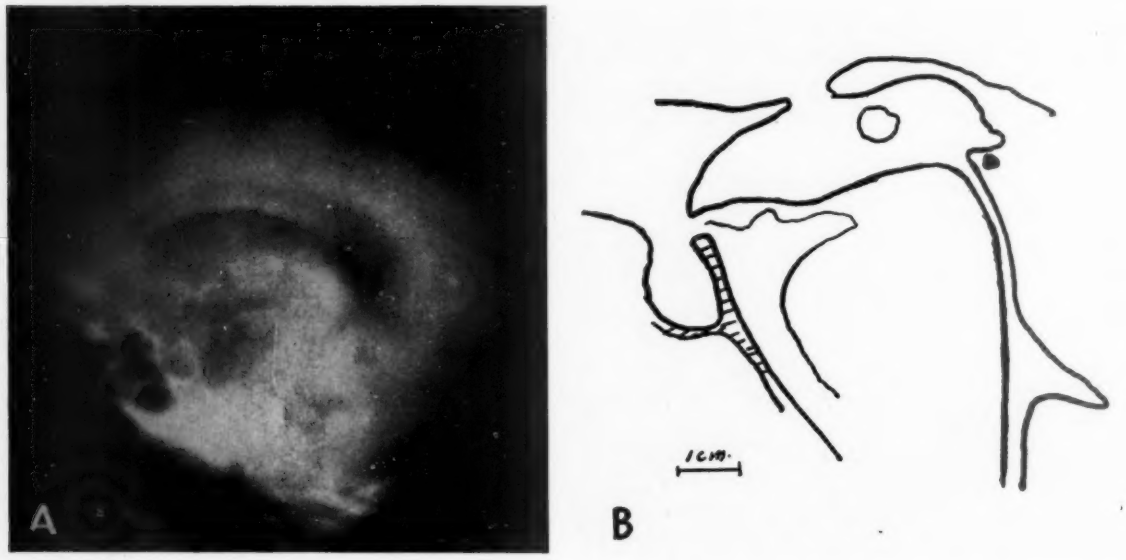

Fig. 3, *A* and *B*. Normal third ventricle, aqueduct of Sylvius and fourth ventricle. Midline laminagram and line drawing to scale.

the configuration of the posterior part of the third ventricle.

The lateral walls are formed by the medial surfaces of the thalami and the hypothalami. These are best seen in the frontal projections. Crossing the chamber at about its midpoint and just behind the posterior lip of the foramen of Monro is the middle commissure. This may be oval or circular in shape and is variable in size. At times it may be sufficiently large to prevent gas from rising to the roof of the third ventricle.

Visualization of the third ventricle is

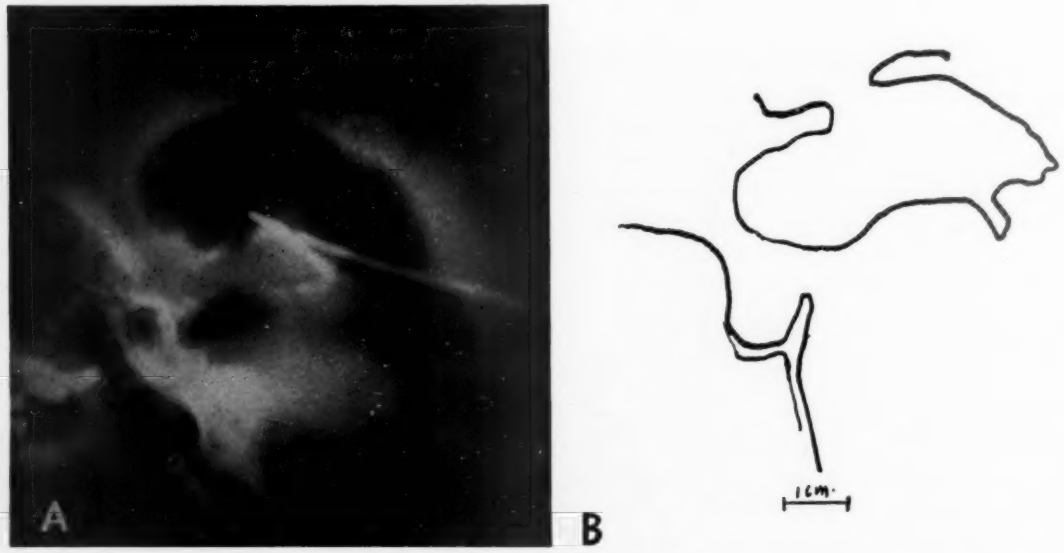

Fig. 4, *A* and *B*. Midline laminagram showing third ventricle and upper part of aqueduct of Sylvius in patient with cerebellar tumor. The distance from the foramen of Monro to the aditus is shortened, and the distance from the anteroinferior angle of third ventricle to the suprapineal recess is increased. The anteroinferior angle is blunted and rounded.

usually more satisfactory with the patient in the recumbent position. Laminagraphy is a distinct aid in the study of this structure, and if filling is incomplete further examination with the brow up or brow down to pass the gas into the anterior or posterior aspects of the third ventricle may be required. The anteroinferior angle is usually better demonstrated in the decubitus than in the erect position, while the roof of the third ventricle and the suprapineal recess may be seen better in the erect posture.

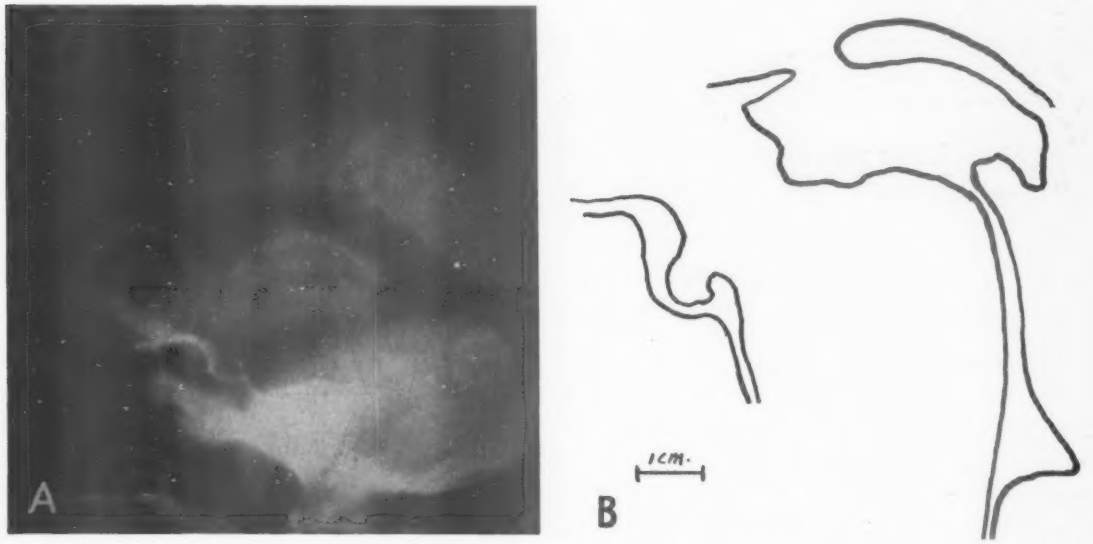

FIG. 5, *A* and *B*. Midline laminagram showing impingement on anteroinferior angle of third ventricle by dermoid tumor. The distance between the foramen of Monro and the aditus is normal, and the distance between the anteroinferior angle of the third ventricle and the suprapineal recess is shortened. The angle is deformed.

THE AQUEDUCT OF SYLVIUS

The opening of the aqueduct into the third ventricle is a small circular orifice measuring about 2 mm. in diameter. There may be a slight funnel shaped configuration at the junction of these structures. Thence the iter passes dorsally and downward, presenting a smooth curve in its upper third continuous with the floor of the third ventricle. Its communication with the fourth ventricle is tapered ventrally while its dorsal aspect is continuous with the floor of the fourth ventricle. The aqueduct is situated between the corpora quadrigemina and the tegmenta, and its average length is 3 cm.

Visualizations of the aqueduct have been more satisfactory in the lateral decubitus positions, but if an adequate amount of gas is present it may also be seen in the erect positions.

THE FOURTH VENTRICLE

As seen in the lateral projection, the fourth ventricle assumes a triangular configuration. Its floor lies perpendicular to a line drawn along the hard palate and continued dorsally in most of the cases studied. In a few patients with long narrow skulls there is a slight forward inclination of the fourth ventricle. Its posterosuperior wall presents a gentle curve inward, and is formed by the superior cerebellar peduncles. The posteroinferior aspect presents a variable gentle curve inward formed by the nodulus, upon which is situated the choroid plexus. The fastigium is formed by the junction of these walls. The floor is formed by the dorsal aspect of the pons and medulla oblongata. The lateral recesses, best seen in the frontal projections, corre-

TABLE I

Distance	Lower Limit	Upper Limit	Mean	Davidoff-Dyke Measurement
A–A′				
Suprapineal recess to chiasmal recess	4.2	4.7	4.4	
B–B′				
Foramen of Monro to aditus	2.8	3.2	3.0	2.6
C–C′				
Aditus to posterior clinoids	3.0	4 0	3.5	*
D–D′				
Suprapineal recess to aditus	0.5	0.6	0.5	
E–E′				
Height of third ventricle	1.3	1.9	1.5	1.42
F–F′				
Diameter of aqueduct	0.1	0.2	0.2	0.15
G–G′				
Midaqueduct to posterior clinoids	3.6	4.5	3.9	3.44
H–H′				
Floor of fourth ventricle to dorsum	3.0	4.0	3.4	3.61
I–I′				
Fastigium to floor	1.5	2.0	1.6	1.46
J–J′				
Fastigium to base	3.0	3.6	3.4	3.26
K–K′				
Diameter at foramina of Luschka	2.0	2.8	2.6	

* Hyndman reported the distance from the aqueduct of Sylvius to the middle of the sella turcica as 4.2 cm. (*Arch. Surg.*, 1938, *36*, 245–291).

spond to the foramina of Luschka. This is the widest portion of the floor, which tapers above and beneath to continue with the aqueduct of Sylvius and the spinal canal respectively.

MEASUREMENTS

Linear measurements were made of the third ventricle, cerebral aqueduct and fourth ventricle. The points of reference are listed below, and the results are arranged in Table 1, together with those reported by Davidoff and Dyke.

A–A′.—from the anteroinferior angle of the third ventricle to the furthermost point of the suprapineal recess.

B–B′.—from the anterior lip of the foramen of Monro to the aditus of the sylvian aqueduct.

C–C′.—from the aditus to the aqueduct to the tip of the posterior clinoid processes.

D–D′.—from the suprapineal recess to the inferior lip of the aditus of the sylvian aqueduct.

E–E′.—the vertical height of the third ventricle was measured from the midpoint of the roof perpendicular to the floor.

F-F′.—the diameter of the aqueduct at its mid-point.

G–G′.—from the midaqueduct to the tip of the posterior clinoid processes.

H–H′.—from the floor of the fourth ventricle at its midpoint perpendicularly to the dorsum sellae.

I–I′.—from the fastigium to the floor of the four ventricle.

J–J′.—from the fastigium to the floor of the inner surface of the posterior fossa perpendicularly.

K–K′.—the distance between the foramina of Luschka as seen in the frontal projections.

COMMENT

The measurements reported here may be considered as representative of the normal linear measurements of the midline chambers of the brain. They are in fair agreement with those reported by Davidoff and Dyke, and the differences may be due to slight differences in the points of reference taken for the various diameters. By means of comparison of similar measurements

made in patients suspected of brain disease which might alter the shape and size of the various structures discussed here, early variations of some clinical importance might be established. As an example, the measurement from the foramen of Monro to the aqueduct of Sylvius was found to be 3 cm. Upward protrusions of the brain stem and herniations through the tentorium cerebelli might be expected to result in a shortening of this distance. In reviewing the series of cerebellar tumors available to me, several instances were encountered in which the distance was shortened by measurement but which had been overlooked by reliance on visual estimation alone.

The measurement from the anteroinferior angle of the third ventricle to the tip of the suprapineal recess is somewhat more variable, probably because of variations in the size of the suprapineal recess. Measurements above the upper limit of normal, however, might indicate lengthening of the third ventricle such as occurs with early hydrocephalus. This, too, was noted in several cases of posterior fossa tumors. Of some interest was the observation that the *A–A'* measurement may increase while the distance between the foramen of Monro and the aditus (*B–B'*) remains within average limits. The anteroinferior angle of the third ventricle may be blunted or rounded when its length is increased.

The distance between the suprapineal recess and the aditus of the aqueduct was determined to see whether any change might occur when upward protrusion of the brain stem occurred. This was not noted in the cases of posterior fossa tumors available, and from the diagrams published by Ecker[3] showing the third ventricle in 2 cases with posterior fossa tumors superimposed on a normal third ventricle one gets the impression that this distance remains constant even though other changes occur in the third ventricle.

The iter-posterior clinoid distance was also determined to see if any changes occurred here with brain tumors. Ecker's drawings indicate this possibility, but similar changes were not encountered in my material.

The position of the aqueduct of Sylvius in relation to the posterior clinoid processes might indicate forward or backward displacement better than could be established by visual inspection alone. It might prove helpful in evaluating such displacements when encountered with midline cerebellar or other posterior fossa tumors.

The measurements of the fourth ventricle found in the present series correspond quite closely with those of Dyke and Davidoff. The purposes of these measurements were adequately discussed by these authors and do not require repetition other than to reiterate that movement of the fourth ventricle may indicate rather precisely the location of a posterior fossa mass.

SUMMARY

Variations in the pneumoencephalographic configurations of the third and fourth ventricles and cerebral aqueduct are discussed, and normal measurements of these structures are reported.

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ROENTGENOLOGIC VISUALIZATION OF THE SEMICIRCULAR CANALS IN A CASE OF PAGET'S DISEASE*

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A GREAT number of articles have been written, which discuss fully the many known aspects of Paget's disease (osteitis deformans).[1,2,3,4,5] The changes produced in the skull are characteristic. The vault is markedly thickened, blotchy in appearance, with a loss of outline of the internal and external tables, and oval or circular areas of increased density. Involvement of petrous bone has been of great interest to both the otologist and the roentgenologist. This case of Paget's disease is being presented because of a unique roentgenographic finding in the petrous bones of the skull.

CASE REPORT

L. S., a white female, aged fifty-five, had no complaints until six months before being seen in the outpatient department of this hospital. During this period she had noticed a gradual, painless curving of her left forearm. There was no history of recent or old trauma, or any previous disease relative to this deformity. Her past history was essentially negative except for infrequent, moderately severe, generalized headaches of short duration. Preceding her two deliveries, twenty-one and eighteen years ago, she experienced prolonged and difficult labors.

FIG. 1

Physical examination was essentially negative except for a posterior bowing of the left forearm. This was not tender. No other obvious skeletal deformities were present.

Laboratory studies revealed the serum calcium and inorganic phosphorus to be within normal limits, 9.6 mg and 3.5 mg. per 100 cc. respectively, and the alkaline phosphatase was elevated to 25.1 units.

Roentgenographic studies of the osseous system disclosed a polyostotic form of Paget's disease involving the pelvic bones, both femora, the left radius and ulna, and the skull (Fig. 1). The bones of the pelvis were thick and massive with marked alteration of the texture. Coarse striae were apparent, producing a fibrillary structure throughout the bones. There was thickening of the cortex of the pubis and ischium.

FIG. 2

* From the Department of Radiology of the Beth Israel Hospital, New York, New York.

The roentgenologic examination of the left radius revealed it to be bowed outward. There was marked thickening of the cortex, associated with irregular areas of destruction of bone.

Roentgen examination of the skull in the Towne position (Fig. 2) revealed a remarkably clear visualization of the semicircular canals of the inner ear, bilaterally. Laminagraphic studies of the skull in the lateral position also clearly demonstrated the canals, on both sides (Fig. 3).

Audiometric studies, performed by Dr. Ralph Peimer, disclosed mild to moderate perception deafness. Both eardrums showed no evidence of any pathological condition. Caloric testing of the vertical and horizontal semicircular canals, bilaterally, gave normal reactions.

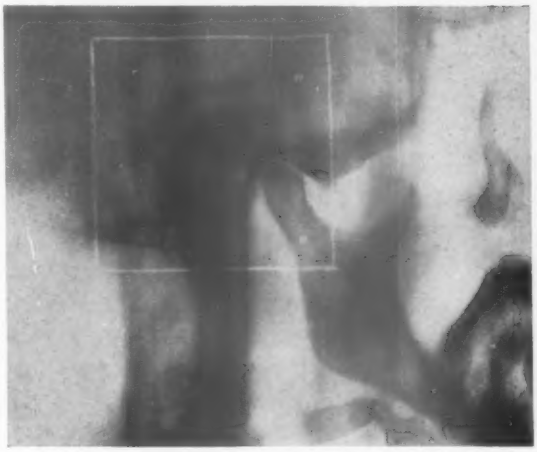

Fig. 3

DISCUSSION

The roentgenographic demonstration of the semicircular canals in Paget's disease, to our knowledge, has not been described in the literature. The excellent visualization of the semicircular canals in this case is probably due to the marked osteoporosis of the temporal bones and to the increased osteosclerosis of the osseous labyrinths of the inner ears.

Deafness, in Paget's disease, is not the result of compression of the auditory nerve, but of marked involvement of the petrous portion of the temporal bone, leading to damage of the inner ear.[6,7,8,9] In spite of these marked changes in the structure of the petrous portion of the temporal bones, in this case, the absence of any marked degree of deafness is noteworthy.

In view of the common occurrence of Paget's disease it is interesting to note that this roentgenographic finding has not been previously reported.

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INFANTILE CORTICAL HYPEROSTOSIS*†

REVIEW OF THE LITERATURE AND REPORT OF FIVE CASES

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and
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THIS curious and little understood disorder was first recognized in 1930 by Roske.[9] He described a male infant who had painful deposits of subperiosteal new bone about both humeri, both tibiae, both radii, and the left mandible. In his careful investigation Roske ruled out tuberculosis, rickets, lues, and scurvy, discussed many other possibilities, and concluded that he was dealing with a new syndrome.

In 1945 Caffey and Silverman[2] described 4 more cases of "infantile cortical hyperostoses." Their paper aroused considerable interest, especially because shortly thereafter Smyth, Potter and Silverman[12] reported on 7 children whom they considered as belonging to the same group. Four of their cases are undoubtedly similar to those described by Roske and by Caffey; 3 can certainly be questioned. In 1946 Caffey[3] added 5 more cases (including the one subsequently reported by Whipple[15]). Since that time there have been five other articles reporting 7 patients.[5,6,7,11,13] If the 3 questionable cases are excluded, the total number now reported is 22. This would indicate that, whether the disorder is a new entity or an old one which was long unrecognized, it is at present not uncommon.

As the number of reported cases has grown, original impressions have naturally had to be modified. There is as yet no clue as to the etiology of this disorder, but there is a growing mass of data which effectively excludes many possibilities. Although "infantile cortical hyperostosis" is being encountered with increasing frequency, it is still often confused with other diseases. Therefore, it seems worth while to review what is known and to add to the literature some facts learned from 5 more cases.

CLINICAL COURSE

Although 2 of Caffey's patients had their first symptoms at eighteen and twenty months respectively, and 1 of ours at six months, all of the others became ill within the first four months of life.

The initial symptom is usually irritability which is often, but not invariably, associated with fever. The patient soon develops firm, tender swellings which seem to be situated deep in the soft tissues. These swellings are diffuse and brawny and are neither hot nor red. They are not associated with adenopathy and they are never fluctuant. Some time after the swellings are evident, deposits of subperiosteal new bone, both in the areas of swelling and also in some apparently uninvolved regions, are demonstrable roentgenologically. These deposits may be too small to be felt or they may be massive so as to produce gross enlargement of a limb. They have been recognized in all parts of the skeleton except the phalanges, the small bones of carpus and tarsus, the vertebrae and the pelvis.

Associated findings which may or may not be present include anemia, leukocytosis with increased sedimentation rate, fever and pleurisy. It has been thought that pleurisy accompanied rib involvement, but 2 of our patients had such involvement with no signs of pleurisy. The disease runs its own course, unaffected by any therapy so far tried, and eventuates in a spontaneous cure, although bowing, especially of the tibia, may persist for some time. It is often

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† This study was supported in part by the Home for Destitute Crippled Children and by a grant from the Douglas Smith Foundation.

characterized by many remissions and exacerbations. When multiple lesions are present they are not all in the same stage of development. As a matter of fact, lesions may be regressing in one part of the body while they progress in another.

In no reported case has there been any evidence of disease in the parents. All patients who were tested had negative tuberculin tests and negative serological findings. No patient had signs of rickets or scurvy, and none responded to trial therapy for these diseases. Irradiation, antibiotics, transfusions and antihistaminic drugs have likewise been without effect.

CASE REPORTS

Case I. M. P. This child (seen through the courtesy of Dr. Vida Wentz of Chicago) was born four weeks prematurely (2,285 grams) after an uneventful pregnancy. Physical examination disclosed no significant abnormalities. The day after birth a blood count revealed 5.2 million erythrocytes, 9,600 leukocytes, with 32 per cent polymorphonuclears and 68 per cent lymphocytes.

The baby was entirely breast fed and did well for the first nine days. On the tenth day of life she suddenly developed a fever (38° C.) for which no cause could be found. On the following day the temperature rose to 38.4° C. and a tender, indurated swelling appeared over the left side of the face. This swelling covered the mandible but did not involve the pre- or postauricular areas. The baby appeared to have pain on motion of the jaw, but did not seem acutely ill. A roentgenogram of the jaw revealed no definite changes. With the diagnosis of parotitis, the child was treated with penicillin.

All constitutional symptoms subsided within forty-eight hours, but the facial swelling persisted. It gradually became more discrete and less tender. When the child was discharged on the twentieth day of life the mass was described as "large, hard—both over and below left mandible."

One month later roentgenograms made at the Children's Memorial Hospital showed a hyperostosis over the left mandible which extended from the angle to the chin (Fig. 1). No treatment was given and the mass subsided gradually. It had disappeared by the time the child was two months old.

Fig. 1. Case I. Roentgenogram shows large deposit of subperiosteal new bone at the angle of the left mandible and a smaller amount extending anteriorly to the symphysis.

Re-examination when the child was ten months old revealed no abnormalities.

The parents of this child, both thirty-one years old, knew of no diseases in themselves, their families, or in their other child, a boy of three. There was no history of allergy. The mother is Rh negative. Diet of mother and baby had been normal and adequate. In this patient the onset of symptoms was earlier than in any of the cases yet recorded.

Case II. G. G. (seen through the courtesy of Dr. Harry Faulkner of Chicago), was born spontaneously after a normal pregnancy. He was perfectly well until he was four months old when he suddenly developed bilateral massive swellings over both cheeks. He was irritable, cried a lot, and vomited several times. A few

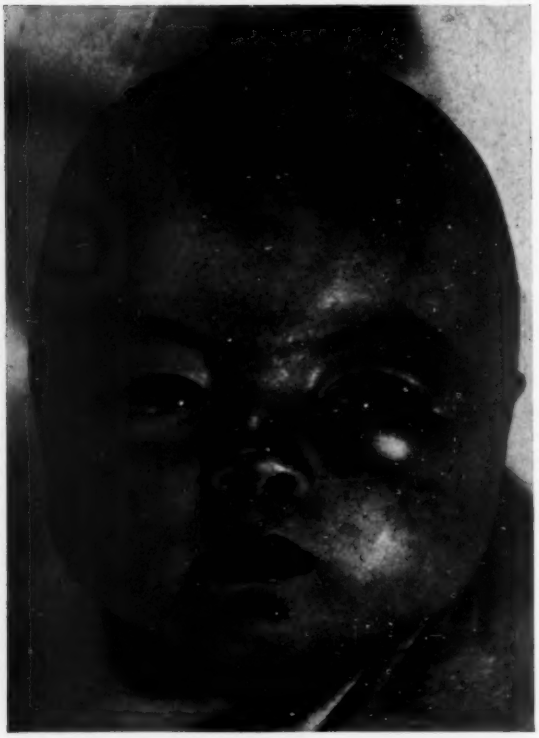

FIG. 2. Case II. Typical facial appearance of fourteen week old infant with infantile cortical hyperostosis of both mandibles.

days later he developed a fever which ranged between 101 and 102° F.

Two weeks later, when he was admitted to Children's Memorial Hospital, he had not improved. The most striking finding was the marked brawny swelling of the face (Fig. 2). Similar swellings were noted over the left clavicle and over both legs. Blood count revealed hemoglobin 6.8, 3.14 million erythrocytes, 27,500 leukocytes with 60 per cent polymorphonuclears.

Roentgenograms demonstrated marked skeletal changes in the mandible, the left clavicle, both humeri and most of the ribs. There was no evidence of pleurisy (Fig. 3). Other bones were not examined.

Further laboratory investigations revealed serum non-protein nitrogen 25, calcium 9.8, phosphorus 4.7, vitamin C 0.1 mg. per 100 cc. The urine was normal. The child was treated with small transfusions, with penicillin and sulfadiazine. When the diagnosis of infantile cortical hyperostosis was made antibiotics were stopped so that the child received them for only three days. During the ten days that he was in the hospital the swellings increased and the temperature remained elevated.

Following his discharge the baby improved gradually and by the time we first saw him, when he was eight months old, he was asymptomatic. Physical examination was normal except that his head and face seemed large for the size of his body, but roentgenograms revealed well organized localized nodular areas of subperiosteal new bone at the angle of each mandible, over the right ulna, the left femur, the right tibia, and fibula.

The twenty-one year old parents of this child and his two and one-half year old brother were all well and had had no serious illnesses. They were all Rh positive. The mother's father and two paternal uncles were known to have tuberculosis but the baby's tuberculin test was negative. Both the mother's brother and sister had well established allergies. It was also reported that the mother, when she was three months pregnant with the patient, had had a vaginal infection which had been treated with sulfa drugs. The diet of both mother and baby had been normal and adequate.

Of the laboratory tests carried out for this child none was significantly abnormal. These included serological examinations, serum calcium, phosphorus, phosphatase, vitamin C and proteins; spinal fluid examination, sternal puncture, agglutination tests for typhoid, paratyphoid, *Brucella*, and cold agglutinins, urinary ketosteroids, and cultures of nose, throat and blood.

CASE III. J. H. This child was born normally at term. She was quite well until she was five weeks old when she became irritable and refused to eat. Shortly thereafter the right leg was found to be swollen and tender. When hot packs gave no relief and the swelling increased in size, the child was brought to the hospital. Examination revealed only bluish pallor and the firm fusiform swelling of the right leg which was 3 cm. larger in diameter than the left. The swelling was tender and evidently caused pain when any attempt was made to extend the knee. There was no fever. Roentgenograms revealed early "hyperostoses" on many bones, but that on the right tibia was the only one large enough to be palpable.

A few days later a biopsy was made of the right tibia. The periosteum was markedly thickened and had a gelatinous appearance. From it there extended dense fibrous bands

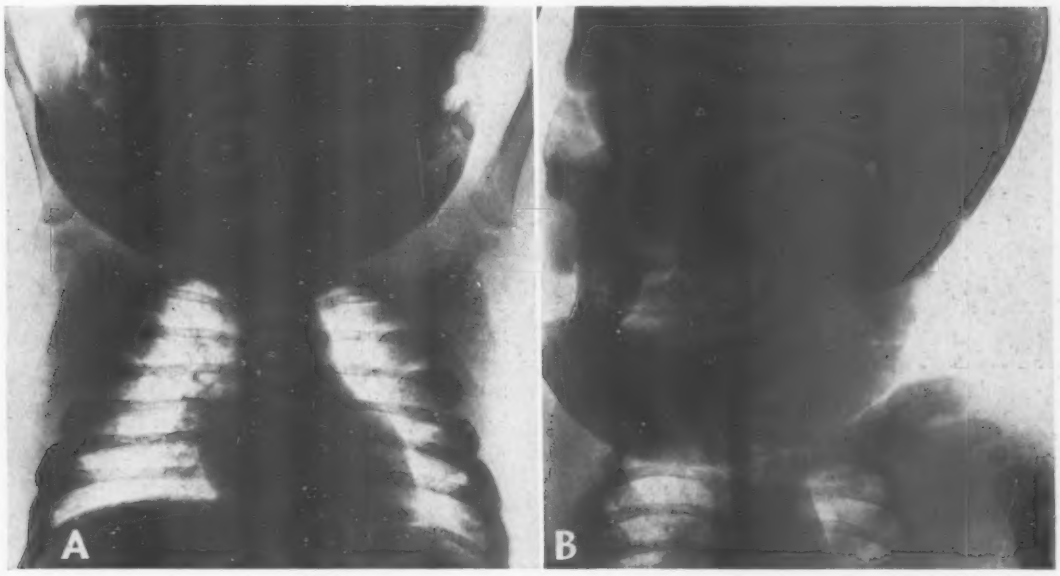

Fig. 3. Case II. Roentgenograms of same infant as in Figure 2. (*A*) All ribs are surrounded with a layer of new bone, but there is no sign of pleurisy. Note massive soft tissue shadow of lower jaws and new bone along both humeri and scapulae. (*B*) Gross enlargement of left clavicle. The outlines of the old cortex are visible through the mass of new bone.

which blended with the fascia investing the muscles and ran out into the skin. The tibia beneath was completely surrounded by a thick layer of new bone which split from the old cortex as it was being removed. There was, within the old cortex, a small medullary cavity which contained red marrow.

Microscopic examination revealed a periosteum which was grossly thickened, edematous, vascular and cellular, though there was nowhere any evidence of active inflammation or hemorrhage (Fig. 4). Figure 5 shows the entire thickness of the cortex and new bone removed from the tibia. A higher power photomicrograph (Fig. 6) shows the unorganized trabeculae of new immature bone. The marrow is fibrous and extremely vascular. There are numerous osteoblasts, as one would expect, but the number of osteoclasts is surprising in view of the fact that the patient was forming new bone at such a rapid rate. The bone of the old cortex

Fig. 4. Case III. Photomicrograph shows edematous collagenous thickening of periosteum with no evidence of hemorrhage or inflammation.

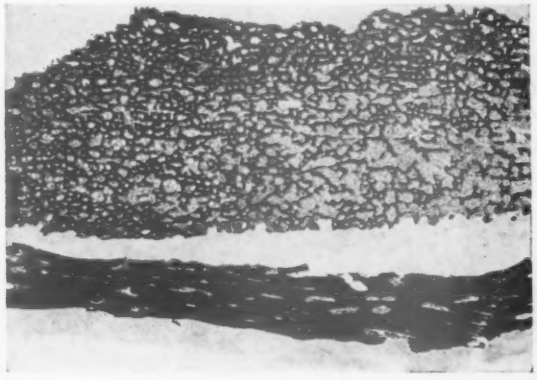

Fig. 5. Case III. Photomicrograph shows the new subperiosteal bone to be three times as thick as the old cortex (the two split from each other in removal but are mounted in normal relationship).

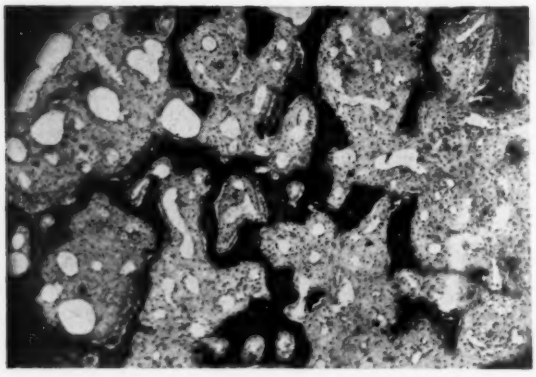

FIG. 6. Case III. Photomicrograph shows detail of the new immature bone. The marrow spaces are filled with loose fibrous tissue which contains a great number of vessels. The number of osteoclasts is surprising since the patient was at this time in the most active bone-forming stage of the disease.

is quite normal. The marrow was examined by Dr. Mila Pierce who reports that the predominating cell type is a small lymphoid cell which has the structure of a micromyeloblast.

Ten days later the size of the leg had increased by half. From then on the disease pursued an irregular course, always afebrile. The child was at all times thin, pale and underweight. At times she had so much pain that even stroking her skin caused her to cry out. There was, at one time or another, involvement (detectable clinically and roentgenographically) of the right tibia and fibula, both femora, multiple ribs (without evidence of pleurisy), both clavicles, both humeri, both radii (with no involvement of ulnae—a new observation), both scapulae, both mandibles. Not all of these appeared at the same time. Often a new lesion appeared while others seemed quiescent; then, at some other time, the quiescent lesions would again swell and become painful. The child could not straighten her hips, knees, or elbows, and attempts to do so caused pain. Because of this the baby did not sit up until she was eleven

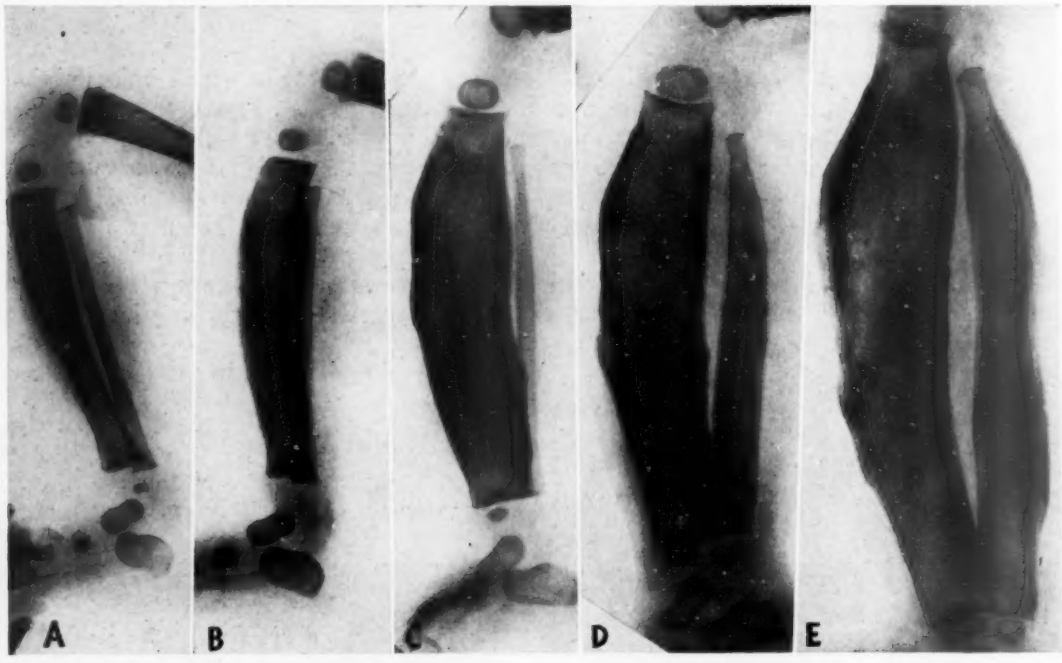

FIG. 7. Case III. Roentgenograms of right leg. (*A*) Two weeks after onset of symptoms there is the shadow of new bone surrounding three-fourths of the tibial shaft. Other bones appear normal. (*B*) Eighteen days later the new bone has doubled its thickness and begins to assume a lamellated appearance. The tibial metaphysis and the entire fibula are uninvolved and the lines of the old cortex are still visible. (*C*) Four months after (*A*), the old cortex has disappeared and the medullary cavity has expanded. New lamellations have been laid down on the periphery and they now extend from one epiphysis to the other. (*D*) Six months after (*A*), the medullary cavity has expanded so as to absorb from within some of the lamellae seen in (*C*). The tibia appears osteoporotic, and the fibula is now grossly involved. (*E*) Twenty-one months after (*A*), there is no further new bone. The metaphyses of both tibia and fibula are assuming a more normal appearance.

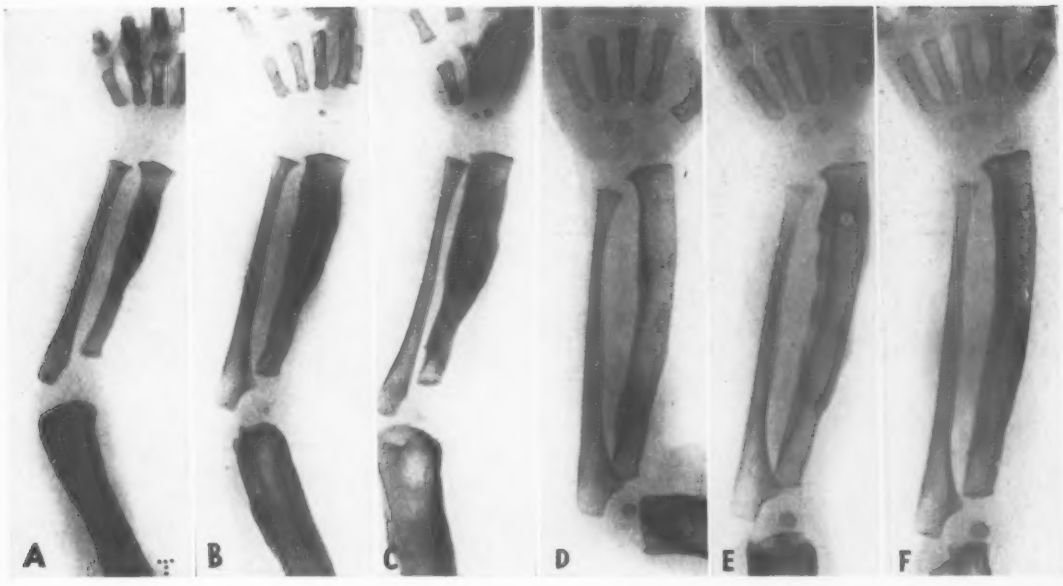

Fig. 8. Case III. Roentgenograms of right forearm. Note that the radius and humerus alone are involved throughout the course.

(*A*) At onset (cf. Fig. 7*A*). The midshaft of the radius is surrounded by new bone, as is the lower end of the humerus.

(*B*) Seven weeks later, new bone about the radius has increased in length and in thickness. The old cortex has begun to disappear. Note that the ossification center for the capitellum is already present.

(*C*) Twelve weeks after (*A*), there is an additional layer of new bone around the radius and the lower humerus. The old cortex has almost disappeared, but the outline of the bones as they appeared in (*B*) can still be seen.

(*D*) Twelve months after onset there has been extensive recession of the new bone. The radius has assumed a nearly normal shape though it is still large. The medullary cavity has expanded so that the cortex is very thin and the bone appears osteoporotic. Ossification centers for bases of phalanges, which usually appear at about eighteen months of age, are already present at thirteen months.

(*E*) Two months after (*D*) (fourteen months after onset), an exacerbation of local symptoms was accompanied by the formation of more new subperiosteal bone on both radius and humerus.

(*F*) Two months after (*E*), recession and reorganization are again evident. At present, twenty-three months after onset, the appearance is about the same.

months old and crawled only at fourteen months. She began to stand with support at twenty months.

Some idea of the evolution of the roentgen picture can be gained from following serial roentgenograms of certain bones. It is of interest that although general development was retarded, bone age was advanced. Figures 7 and 8 show one upper and one lower extremity at varying times after the onset of the initial symptoms. The most striking thing is the way in which successive layers of subperiosteal new bone are laid down to surround the old bone completely. Each layer corresponds in time to an exacerbation of the local symptoms. No matter how much new bone is formed, it never extends beyond the epiphyseal line. The old cortex appears to be gradually absorbed from within so that the medullary cavity enlarges proportionately to the circumferential increase of the whole bone. When the disease begins to abate, this sequence is reversed. No new bone is formed on the periphery, and this, in conjunction with the absorption from within, results in a wide bone with a thin cortex. Thus the bone, although it is grossly enlarged, appears osteoporotic. From this time on, if there is no exacerbation, there is a gradual decrease in size of both periphery and medullary cavity until the normal architecture is reconstituted. This reorganization is apparent on the roentgenogram long after the clinical symptoms have disappeared, and the osteoporosis may persist for many months.

Several times during the most active phases of this child's disease she was hospitalized for

FIG. 9. Case III. Photograph of patient at twenty-two months showing gross irregular enlargement of right lower extremity.

study. There was never any fever or elevation of sedimentation rate. The lymphocytes ranged between 10,000 and 15,000 but there was no alteration in the differential picture. The baby and both parents are Rh positive. The tuberculin test was negative as was the Wassermann reaction of baby and parents. Heterophile agglutinations and those for typhoid and paratyphoid were negative. Blood cultures produced no growth. Blood chemistry studies, which included numerous determinations of calcium, phosphorus, phosphatase, cholesterol and vitamin C were always within normal limits.

On one occasion (while the disease was very active) an attempt was made to estimate calcium retention. The baby was kept for four days on an intake of 820 mg. of calcium per twenty-four hours. On the fifth day all urine and the stools marked with carmine were collected and analyzed for calcium. There were 580 mg. of calcium in the feces, and 67 mg. in the urine, which would indicate a retention of 170 mg. per twenty-four hours. Obviously, such a limited determination is inadequate but the percentage retention agrees rather closely with the figures for infants given by Macy,[8] who cites a 138 mg. calcium retention on an intake of 721 mg. This is surprising considering the tremendous amount of bone the child was forming at the time the test was made.

At the time of the biopsy of the tibia, material was obtained for bacteriologic studies. Scrapings from both soft tissue and bone were placed on a wide variety of culture media and incubated both aerobically and anaerobically. There was no growth from any of these preparations. Emulsified tissue was filtered for virus study and the filtrate inoculated into the amniotic fluid of ten day incubated eggs, into the cornea and vitreous fluid of a rabbit, into guinea pig testis, and intraperitoneally, intranasally, and intracerebrally in mice. There was no evidence of virus activity and no change was demonstrated in the bones of any of the injected animals.

At present the patient is twenty-four months old and has had her disease for twenty-three months. Except for a prolonged course of an antihistaminic drug (benadryl), which was without discernible effect, no treatment has been given. The baby is generally well, but still has evidence of bone disturbance. The only gross deformities visible are in the right lower extremity (Fig. 9). Although some previously involved bones now appear normal on the roentgenogram (clavicle, mandibles, ribs and scapulae), there are changes still present in all long bones except those of the left leg which have always been normal. The baby weighs only 20 pounds but she is well developed and intelligent. In none of the patients so far recorded has the course of the disease been so prolonged. The younger sister of this patient has had no difficulty.

CASE IV. L. G. (seen through the courtesy of Dr. C. C. Rudolph of St. Petersburg, Florida) is a Negro child whose birth and early development were entirely normal. When he was six months old his right forearm began to enlarge and was extremely tender. He had fever that was

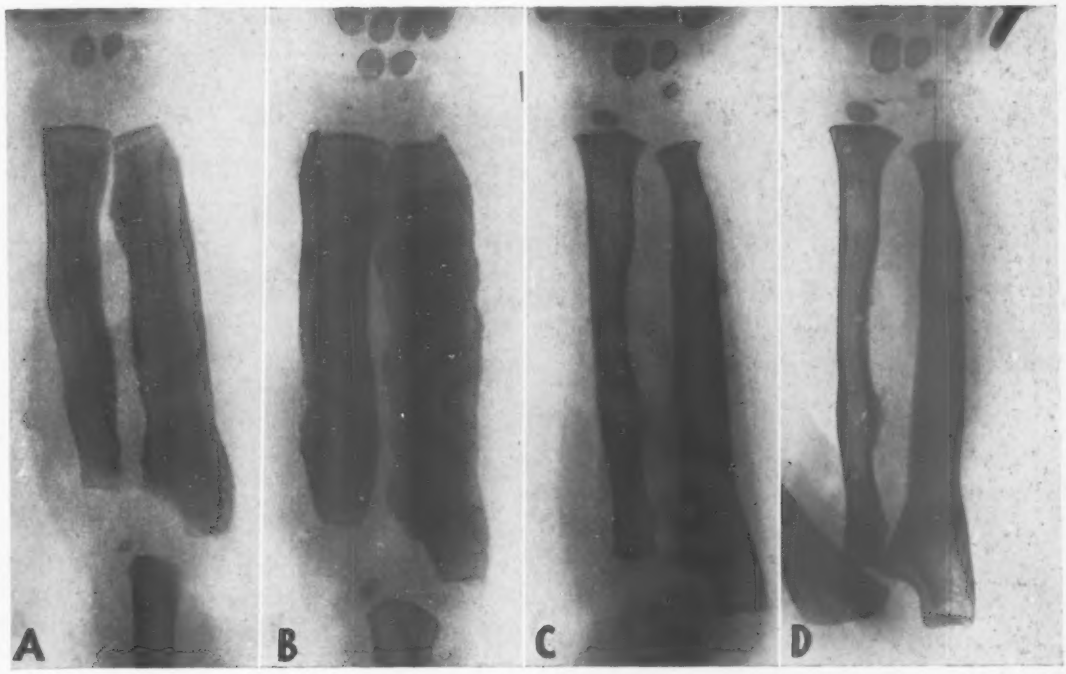

Fig. 10. Case IV. Roentgenograms of right forearm. (*A*) Shortly after onset of symptoms. The normal outlines of the bones are still visible, but are completely encased in a lamellated envelope of new bone of more than twice the width of the normal shaft. Note again that the epiphyses are not involved and that ossification center for the trochlea is already present at six months of age. There are also three centers visible in the carpus. (*B*) Six weeks after (*A*), the new bone is thicker and more irregular, and the outlines of the old cortices have almost disappeared. (*C*) Twelve months after (*A*), there is a residual of new bone on the medial surface of the upper ulna, and a small tuft on the radius. Both bones are larger than normal with thin cortices and generalized osteoporosis. (*D*) Eleven months after (*A*), there is further reorganization of the bones, but slight enlargement and osteoporosis persist. There is still a trace of new bone on the upper portions of both radius and ulna.

occasionally as high as 101° F. The arm grew steadily worse until it was twice the normal size and was so sore that the child did not move it at all. The roentgenogram at this time (Fig. 10*A*) shows the two bones of the forearm completely surrounded by lamellated new bone. Six weeks later (Fig. 10*B*) the mass of bone is larger, more irregular, and the shadow of the original cortex has disappeared in many places.

When we first saw the baby, eight months after the onset of symptoms, his forearm was still obviously enlarged, but was not painful. There were no constitutional symptoms. The roentgenogram (Fig. 10*C*) shows the new bone reduced to a small tuft on the proximal radius and an irregular shadow on the medial surface of the ulna. The bones have resumed a more nearly normal shape, but both are still wider than they should be. This increased circumference is primarily due to an enlarged medullary cavity, for the cortex is, if anything, somewhat thinned producing the appearance of osteoporosis noted in the previous case. There were no other bones involved at any time.

Routine blood count, sedimentation rate, urinalysis, tuberculin test, serological examinations (of both patient and mother), spinal fluid examination, and blood chemistry, including serum vitamin C and phosphatase levels, were normal. The serum calcium was 13 mg. per 100 cc. and the phosphorus 5.0 mg. on one occasion and 6.2 mg. on another. These values are perhaps significant in view of the fact that the disease was resolving.

Biopsy was performed on the involved ulna. The periosteum was thickened and fibrous. Although it could be stripped from the bone without trouble, it blended into a heavy fibrous tissue which surrounded the muscles and sent stringy bands through the subcutaneous fat to the skin. Within this tissue the muscles appeared to be small and pale, but not

FIG. 11. Case v. Photograph at the age of five months shows obvious enlargement of the lower jaws.

scarred or fatty. The bone was grossly normal in appearance except for its size.

Microscopic examination showed the muscle to be abnormal. There is definite degeneration and fibrosis, and the arteries show a peculiar proliferation of the intima. There is no sign of active inflammation but focal collections of small round cells are present.

The periosteum was cellular, showed marked collagenous thickening, and changes in the vessels which, though slight, were similar to those seen in the vessels of the muscle. Neither tissue showed evidence of inflammation or hemorrhage. Even the bone section does not contribute a great deal. The most striking finding is an almost continuous syncytium of very large pale osteoblasts lining the medullary surface of the outermost trabeculae. The marrow is somewhat fibrous. There are no inflammatory cells and no evidence of hemorrhage.

The postoperative course was uneventful and the child's recovery continued. Eleven months after the onset of symptoms the appearance of the forearm was normal, but there were still distinguishable changes on the roentgenogram (Fig. 10*D*).

The parents of this child had been born in and had always lived in Florida. Neither had had any serious illness. There was no history of tuberculosis, venereal disease, or allergy.

CASE v. B. W. was born normally at term after an uncomplicated pregnancy. At three weeks of age she began to be fussy and cried frequently, but no other symptoms were noted until the baby was three and a half months old. At this time swelling of the left cheek appeared, and any attempt to move the head was resisted. During feedings the child cried as if in pain and her mouth would not open fully. After penicillin therapy the swelling seemed to subside somewhat only to appear worse than ever one month later.

When first seen at five months of age physical examination revealed an irritable, pale, fat baby. The child could not open her mouth widely and fussed when any attempt was made to move jaw or head. A hard mass was palpable over the angle and ramus of the left jaw. This was covered by soft tissue swelling which was not hot or discolored. A similar soft tissue swelling was present on the right (Fig. 11). Rectal temperature was 99.8° F., the white blood cell count 17,400, hemoglobin 9.0 and red blood cell count 4.22 million.

Roentgenograms of the jaw (Fig. 12) show laminated subperiosteal new bone along both

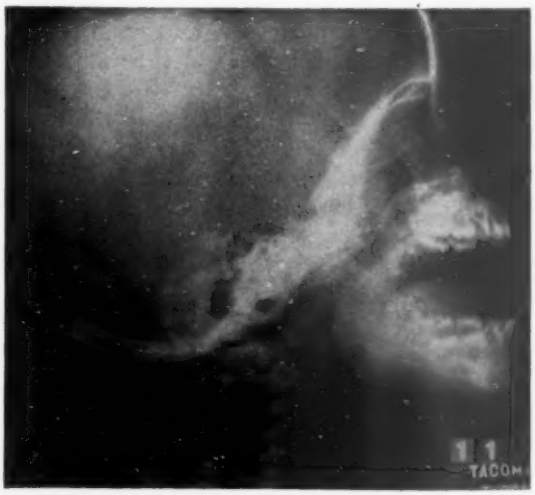

FIG. 12. Case v. Roentgenogram of the jaw shows bilateral deposits of laminated subperiosteal new bone along both mandibles.

mandibles. A survey of the entire skeleton revealed no other bones to be involved. This child is still under observation.

There is nothing abnormal in the past history of this child or the parents. There is no suspicion of allergy, and there were no dietary peculiarities.

COMMENT

Although it is now obvious that infantile cortical hyperostosis is a distinct entity, it is not yet clear whether it represents a new disease. Of course there are suggestive reports in the older literature,[14] but in the absence of roentgenograms it is impossible to prove the true diagnosis of these cases. Even after roentgen examination had become a standard diagnostic procedure almost all skeletal disorders of infancy were attributed to lues. As late as 1938 and 1939 Chiari[4] and Caffey[1] were pointing out that "osteochondritis" and "periostitis" accompany many different conditions of infants and are far from pathognomonic of lues. On the other hand, a search of our own roentgenographic files of the past twenty years revealed no case which remotely resembles those of infantile cortical hyperostosis.

There is apparently no sex preference for the disease. Of the total number of 27 cases there are 15 males and 12 females. Neither race nor geographical location seems to be a factor. Cases have been reported from Holland, from Germany, from Canada, and from eleven widely scattered states in our own country. Twenty-five of these patients were Caucasian, one an American Negro. Recently a case was observed in a Chinese native of Shanghai.[16] Cases have been noted in more than one member of a family, but not simultaneously.

It is clear that infantile cortical hyperostosis is probably not related to rickets, scurvy, lues, tuberculosis, pyogenic infection, allergy or trauma. Although the few virus studies which have been completed thus far have given negative results, further investigations along this line may be warranted.

Thus far the evidence is that the disease is not dependent upon a disturbance of mineral metabolism. In this connection it is surprising to note that no patient has had a markedly elevated alkaline phosphatase level. (This is difficult to evaluate precisely because in many cases the units employed are not designated.) In our own patients repeated examinations have always given normal levels.

Rothman and Leon[10] have recently described periosteal new bone deposits in 2 patients with proved hypervitaminosis A. They have suggested a similarity between these cases and those of infantile cortical hyperostosis although there is no great similarity in the roentgenograms. Furthermore, no patient with infantile cortical hyperostosis has been reported to have any symptoms of hypervitaminosis A and none had a history of abnormal intake.

It seems entirely possible that the disease is not primary in the skeletal system at all. Most patients have constitutional symptoms and soft tissue inflammations long before any bony change is evident. Perhaps the initial disturbance is in muscle or even in vessels which in turn affect the periosteum enough to stimulate it. Such a theory would help to explain the lack of periosteal inflammation or hemorrhage. It would also explain the findings in the few reported muscle biopsies which, like ours, have shown evidence of degeneration and changes in vessels.

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VOL. 63, NO. 2

OSTEOCHONDRITIS DISSECANS OF THE SHOULDER

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THIS case of osteochondritis dissecans is presented because of the rarity with which such lesions are found in the shoulder. In reviewing the literature of the past twenty-five years, we found reports of only 2 such cases—one involving the head of the humerus and the other involving the glenoid process of the scapula.

Perhaps, as Phemister[19] indicates, all the theories as to the etiology of osteochondritis dissecans are open to criticism as to their validity. In general, however, these theories may be divided into those pointing to a traumatic origin and those pointing to a non-traumatic origin. The trauma may be extra-articular and result in small direct fractures (Monroe[3]) or injury to the blood supply of the articular plate (Axhausen[3]) or subchondral impression fracture (Hellström[3]). The trauma may be intra-articular as result of the pull of the posterior cruciate ligament (Barth[3]), or impaction of the tibial spine in the interchondylar ridge (Freiberg[3]). The non-traumatic theories consider the possibility of a bland embolism occluding the arteries supplying the articular plate (Axhausen[1]), or infection of mild degree causing a periostitis (Knaggs[3]). Wagoner and Cohn[23] suggest that heredity may be a significant factor; they point to the significant incidence of this disease in certain families and the frequency of bilateral involvement. Nielsen[18], in a study reporting on 168 cases of osteochondritis dissecans of the elbow joint, points out that the similarity in the pathological picture to Perthes' or Köhler's disease would suggest a similar etiological agent. Littlejohn[15], who had attempted to reproduce osteochondritis dissecans experimentally by trauma, supports the latter thesis.

However, more of the recent studies and analysis accept the traumatic theories as more reasonable.[10,13,16,21]. This is based mainly on the observation that osteochondritis dissecans occurs in the age group which is most subject to trauma and that the articular surface is insensitive to pain. Thus minor trauma may produce injury without giving a history of onset. This has been also suggested in the experiments by Küntscher[12], by reproducing fragmentation of the articular surface similar to osteochondritis dissecans when he subjected the ends of the humerus and femur to rhythmic blows.

The only reported case of involvement of the head of the humerus was that of Salmon[20] in 1923. He reported a case of a white male (age unknown) who fell 6 feet from a scaffold and injured his right shoulder both by the fall and by the falling scaffold. He was examined six weeks following injury, at which time he had limitation of motion of the shoulder and atrophy of the deltoid muscle. A roentgenogram revealed a cloverleaf shaped density at the superior surface of the head of the right humerus with a broad pedicle attaching it to the underlying bone. He was treated by immobilization in a cast for six weeks. Following this time, there was freedom from pain but there was no improvement in the motion of the shoulder. The final diagnosis of osteochondritis dissecans was made on the basis of roentgen evidence of a loose body and no obvious evidence of tuberculosis. More recently, Lavner[13] reported a case of osteochondritis dissecans of the glenoid of the scapula; however, he gave no details on this case.

The pathology and roentgenology of this disease are usually specific. The roentgeno-

FIG. 1. Patient D. B. Roentgenogram taken on March 6, 1946.

gram usually reveals a loose body in the joint with evidence of a niche in the articular surface. There is usually very little sclerosis of the underlying intact epiphyseal bone.[19] Occasionally, the loose body remains in contact with the articular surface and is demarcated by an area of radiotranslucency. König[14] described the pathology as "fragments become separated from the articular surfaces. Bony surfaces of the fragments become covered with dense connective tissue and cartilage. A similar change takes place within the defect from where the fragment originated. At the same time there is slight effusion and villous hypertrophy."

FIG. 2. Patient D. B. Roentgenogram taken on November 13, 1946.

Osteochondritis dissecans has to be differentiated from other forms of aseptic necrosis which occur in the region of joints. In caisson disease[2,7,8,9] it has been found that multiple infarcts of the long bones occur usually in the diaphysis, but they also occur in the epiphysis. In the latter case, Phemister *et al.*[8] report that there is "occurrence of varying amounts of collapse of the weight bearing portions, invasion and replacement by new bone, with calci-

FIG. 3. Patient D. B. Roentgenogram taken on December 6, 1947.

fication of the nonsubstituted portion." Although the case reported herein had been exposed to pressures above atmospheric, a roentgenogram taken at the time of injury revealed no defects. Subsequent films of all the long bones of the upper and lower extremities revealed no pathological condition. It appears more reasonable to assume that the changes in the shoulder of this case are on the basis of loose body formation and subsequent hypertrophic joint changes.

It is more difficult to differentiate this lesion from aseptic necrosis of bone of undetermined etiology. However, these lesions have been described[18,22] as being mas-

sive, involving multiple areas in the long bones and occurring in the older age groups. Taylor[22] describes a typical site of involvement "as an irregular area of altered or decreased density, sometimes, but not always surrounded by a thin linear area of increased density." There is no evidence of similar roentgen changes in the case reported herein.

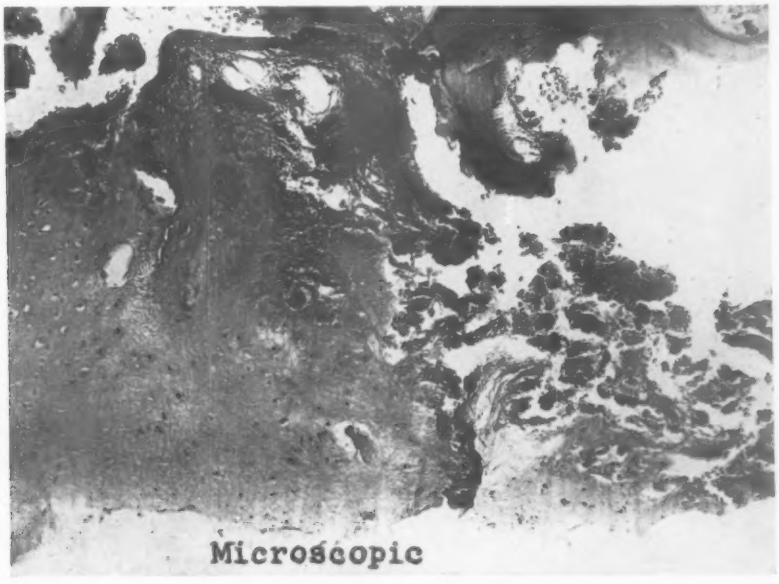

Fig. 4. Patient D. B.

The other possible causes for loose body formation and joint lesions such as tuberculosis, osteoarthritis, synovial chondromas and gouty arthritis have been ruled out by their characteristic findings.

REPORT OF CASE

D. B., male, aged forty, was seen in the office on April 4, 1946, for the complaint of pain and impairment of motion of his right shoulder. He stated that in February, 1941, he was struck on his right shoulder by a swinging load of lumber which was being lifted by a crane. Because of pain, a roentgenogram was taken by a local physician. No pathologic lesion was noted on this film. No further treatment was instituted and the pain subsided. Later he began to have intermittent attacks of pain which became worse on elevating his arms above shoulder level. His complaint became increasingly severe and, prior to his visit, he was unable to lift his right arm above shoulder level. He also began to notice numbness in his right hand and he had lost weight because of loss of appetite. There were no other joint complaints.

In 1936 he fell from a scaffold injuring his right shoulder and fracturing his right wrist. He had worked from 1939 to 1941 in tunnel construction where he was usually exposed to pressures of 15 pounds above atmospheric and worked from eight to twelve hours daily. In 1940 he had two attacks of bends which were quickly relieved by decompression. His attacks were described as general muscle aches. He also developed impairment in hearing which was worse in his right ear. His past family history is non-contributory. He is married and has four children, all living and well.

On physical examination he had good muscular development and appeared younger than his stated age. It was noted that he had active limitation of motion beyond 90° abduction and flexion of his right shoulder. There was moderate atrophy of the right deltoid muscle. A roentgenogram of the right shoulder showed an area of sclerosis on the mesial inferior aspect of the head of the right humerus with detached fragment of articular bone overlying this area. Films taken of the long bones of the upper and lower extremities were negative. Laboratory examinations were negative.

On April 7, 1946, an arthrotomy of the right shoulder was done. The joint cavity revealed softening and loss of normal translucency of the articular cartilage in the inferior mesial aspect of the head of the humerus. This area with its subchondral bone was readily removed with a curet. The patient had an uneventful postoperative course.

The microscopic report: "Sections through fragments of cartilage disclose a moderate degree of degenerative changes. Few atypical bony trabeculae are present along the edges of the cartilage. The fibrocartilage contains few small calcific deposits and in this area is more cellular and presents a moderate fibroblastic proliferation.

"Section through fragments of bone at the costochondral junction disclose rather large bone trabeculae with dense dark staining matrix. An occasional trabecula is surrounded by osteoid tissue. Only few osteoblasts are present and there is very little evidence of new bone formation. The few visible marrow spaces are filled by fibrous connective tissue. Diagnosis: Changes are consistent with osteochondritis dissecans."

The patient was examined at intervals following his operation and moderate improvement was noted. At the time of his last examination, in December, 1947, he was employed as a truck driver and he had no complaint referable to his shoulder. Physical examination showed about a 10° loss of flexion and abduction; about 15° loss of external rotation; and ½ inch loss in the acromial axillary circumference of the shoulder. A roentgenogram revealed smoothing of the articular surface, further decrease in the density in the inferior mesial aspect of the right humerus and moderate lipping of the inferior mesial edge of the joint.

FIG. 5. Patient D. B.

SUMMARY

The literature on osteochondritis dissecans of the shoulder joint has been reviewed. One case of osteochondritis dissecans of the shoulder with its gross and microscopic pathology has been presented.

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ACUTE GASEOUS CHOLECYSTITIS

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ACUTE gaseous cholecystitis or gas phlegmon of the gallbladder, as it has occasionally been designated, is a rare acute inflammatory condition of the gallbladder produced by gas forming anaerobes. The *Clostridium welchii* and the *Bacillus coli* are the organisms most frequently cultured from the infected gallbladder wall and bile. The presence of anaerobic organisms in the gallbladder is not of unusual occurrence. Gordon-Taylor and Whitby[2,3] reported the presence of *Bacillus welchii* in 19 per cent of 100 gallbladders removed at surgery and in 13 per cent of a series of cases in which necropsy was performed. Thorsness[10] demonstrated that these organisms are generally non-pathogenic, non-spore-forming and are of low virulence. Diminished resistance of the tissues as a result of obstruction of the cystic duct, common duct, or of the vascular channels produces a culture medium in which virulence and spore-forming ability is increased, and the symptoms of a severe, acute cholecystitis are produced.

Walters and Kaplan[11] state that within twenty-four to forty-eight hours after the onset of symptoms, the shadow of the gas-filled gallbladder lumen may be demonstrated on a flat plate of the abdomen. Usually a fluid level is present if the patient is placed in the erect position. As infection progresses, the gas infiltrates the gallbladder wall and is seen as a narrow crescentic line just peripheral to the gas-filled lumen. Rupture may produce a gas-filled abscess cavity. If the infection subsides under conservative medical treatment, the gas is absorbed or perhaps expelled through the duct system.

Seventeen cases of acute gaseous cholecystitis have been reported in the literature. Six of these cases were treated surgically, 4 were treated medically without surgical intervention, 1 was treated by roentgen radiation, and the treatment of 6 cases is unknown. Of the cases treated surgically, 3 died. One died of edema and emphysema of the wound and lower thoracic wall, 1 died of a pulmonary embolus, and the third patient apparently never fully recovered from the operation and died in twenty-four hours. One of the operated cases survived and the outcome of 2 cases is unknown. The 4 cases treated medically and the one treated by roentgen radiation all made uneventful recoveries.

Patients who have signs and symptoms of acute cholecystitis, and show roentgen evidence of gas in the gallbladder, present special problems of treatment. Operative intervention may disseminate an otherwise local infection, whereas conservative treatment may be followed by rupture of the gallbladder into the peritoneal cavity. The majority of authors favor conservative treatment of these patients and the above mortality bears out their opinions. McCorkle and Fong[6] believe that the usual interval cholecystectomy should not be performed after subsidence of infection in cases of gaseous cholecystitis.

The case presented in this paper is one of acute gaseous cholecystitis with rupture of the gallbladder and abscess formation.

REPORT OF CASE

W. L., male, white, aged seventy-five, was admitted to the hospital in a confused state and under the influence of narcotic drugs which had been administered by his family physician. He was apparently well until two days previous to admission at which time he developed a sudden, severe, "crushing" pain in the substernal region and mid-epigastrium. The pain radiated down his left arm and was followed by nausea and repeated vomiting. At the time of admission the pain had assumed a constant burning character and had localized in the right side of his abdomen, in both the right upper and lower quadrants. The pain was at no time

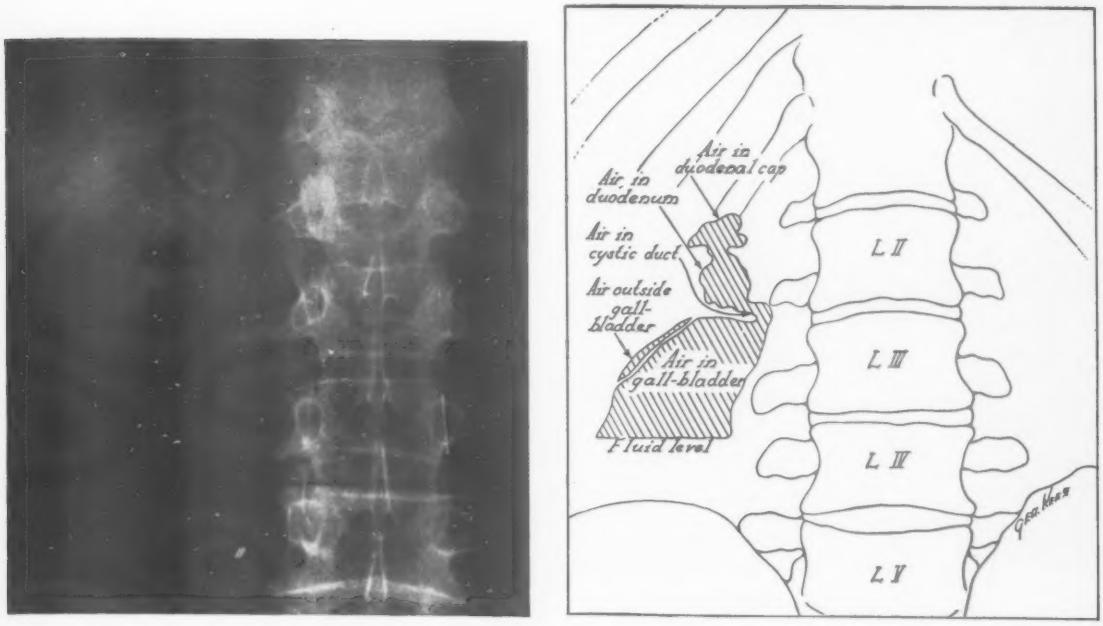

Fig. 1. Anteroposterior roentgenogram of the abdomen, taken in the upright position, using Potter-Bucky diaphragm.

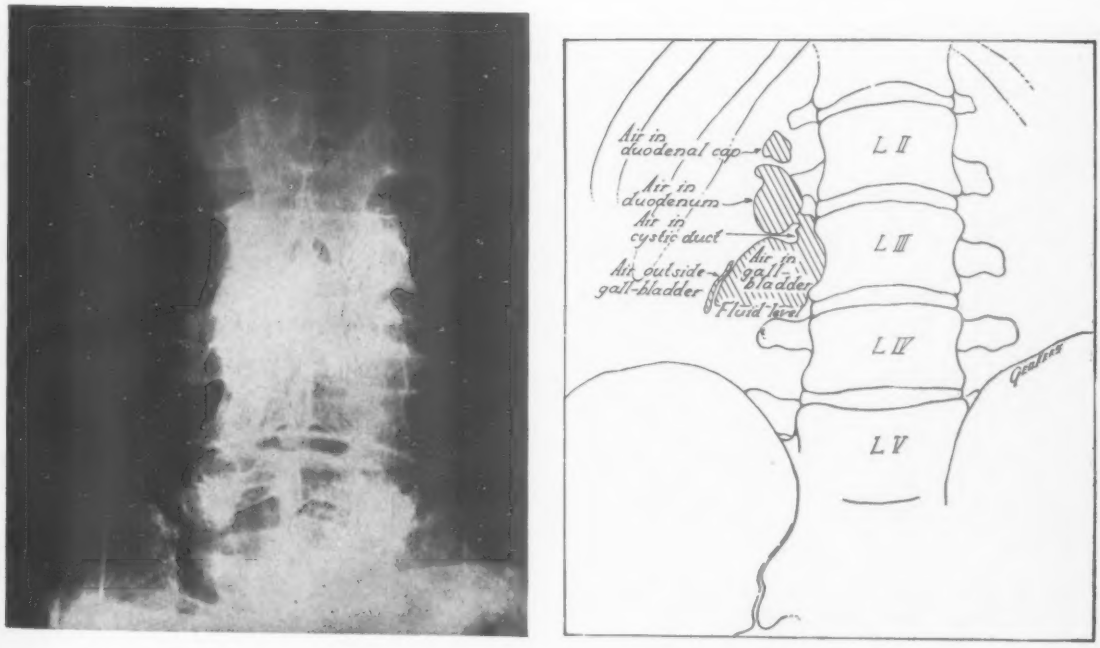

Fig. 2. Another anteroposterior roentgenogram of the abdomen, taken in upright position, using Potter-Bucky diaphragm.

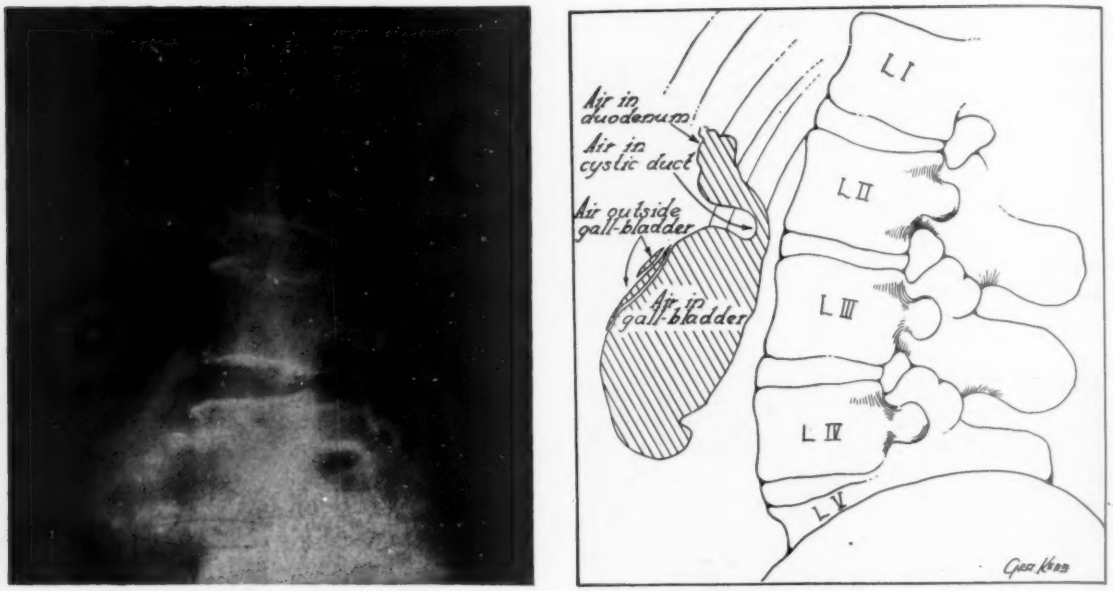

FIG. 3. Lateral roentgenogram of the abdomen, taken with the Potter-Bucky diaphragm, with the patient lying down.

colicky. There had been no distention, no noticed fever, no melena, and no acholic stools. Past history was negative except for a prostatectomy ten years before. The general physical examination approximately forty-eight hours following the onset of symptoms was not remarkable except for the abdomen. The abdomen was not distended and was normal to percussion. The entire right side was rigid and extreme tenderness was present from the right costal margin to the right iliac crest and medially to the midline. Rebound tender-

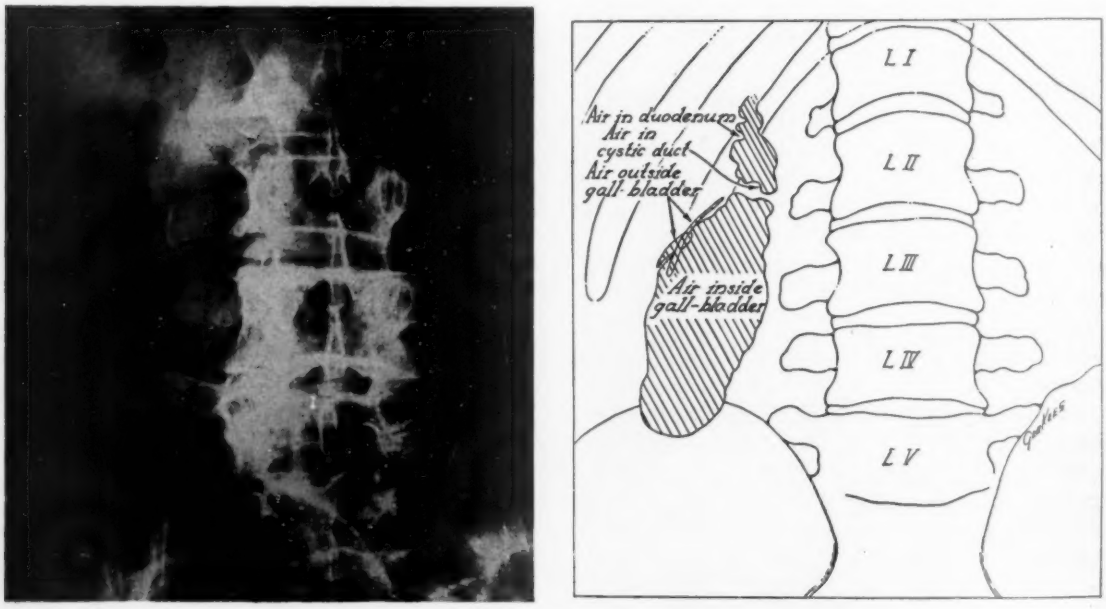

FIG. 4. Anteroposterior roentgenogram of the abdomen, taken with the Potter-Bucky diaphragm, with the patient lying down.

ness was referred to the right side of the abdomen. No masses were palpable. Peristalsis was present and normal. The temperature was 98.6° F. and the pulse rate 100. Blood pressure was 140/90. The white blood cell count was 23,300, with 90 per cent polymorphonuclear cells. The icteric index was 13 units.

Plain and upright roentgenograms of the abdomen taken on January 28, 1948, about forty-eight hours after the onset of illness, showed a gallbladder shadow (acute gaseous cholecystitis with rupture of the gallbladder).

The patient's temperature at the time of admission was 98.6° F. Twelve hours later it rose sharply to 100.6° F. and then to 102° F. He continued to complain of severe pain and required morphine. Penicillin, 50,000 units every three hours, and intravenous fluid containing 2.5 grams of sulfadiazine per liter, were started. He was operated upon as an emergency

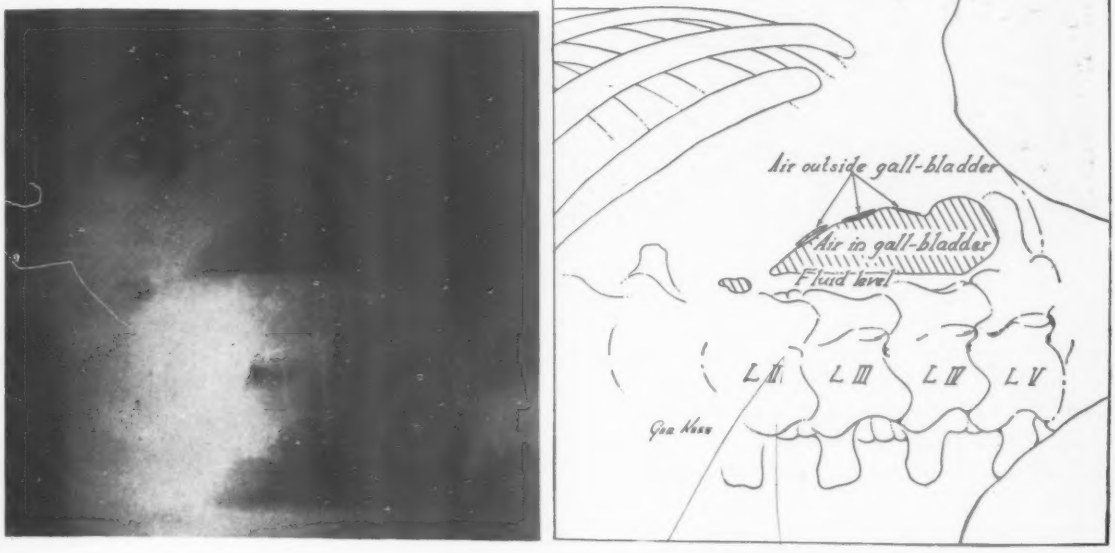

Fig. 5. Roentgenogram taken with the patient in left lateral decubitus.

gas-filled gallbladder which measured approximately 9.0 by 4.5 cm. Peripheral to the contents of the gallbladder lumen, a circumferential fine black line was seen lying parallel but outside the gallbladder shadow. In the upright position a fluid level was seen in the gallbladder with air outlining the gallbladder above the fluid level and also outlining the cystic duct; a spot film of the same area taken in the right lateral view with the patient lying down, shows the entire gallbladder to be outlined with air and also there would appear to be some air within the cystic duct. Similarly, both right and left lateral decubitus films show air again in the gallbladder and we see a linear line of decreased density outside the gallbladder as described above which was interpreted as being air outside the gallbladder. The roentgen diagnosis, prior to operation, was a gallbladder filled with air and fluid with rupture of the gallbladder as was evidenced by the air outside the forty-three hours after admission. The preoperative diagnosis was acute gaseous cholecystitis with rupture of the gallbladder and abscess formation.

When the abdomen was opened, an acute inflammatory mass was encountered. Further exploration demonstrated that the gallbladder wall was black, necrotic and ruptured. A large abscess lay between the gallbladder and the liver. The fluid in the gallbladder and in the abscess cavity was frothy and full of bubbles. A cholecystotomy was done. A large rubber tube was placed in the gallbladder and several cigarette drains were placed in the abscess cavity. Cultures taken from the gallbladder subsequently produced a pure culture of *Clostridium welchii*.

The patient was irrational for three days postoperatively. On the second day he pulled out his drains and his cholecystotomy tube. The wound, however, remained clean and

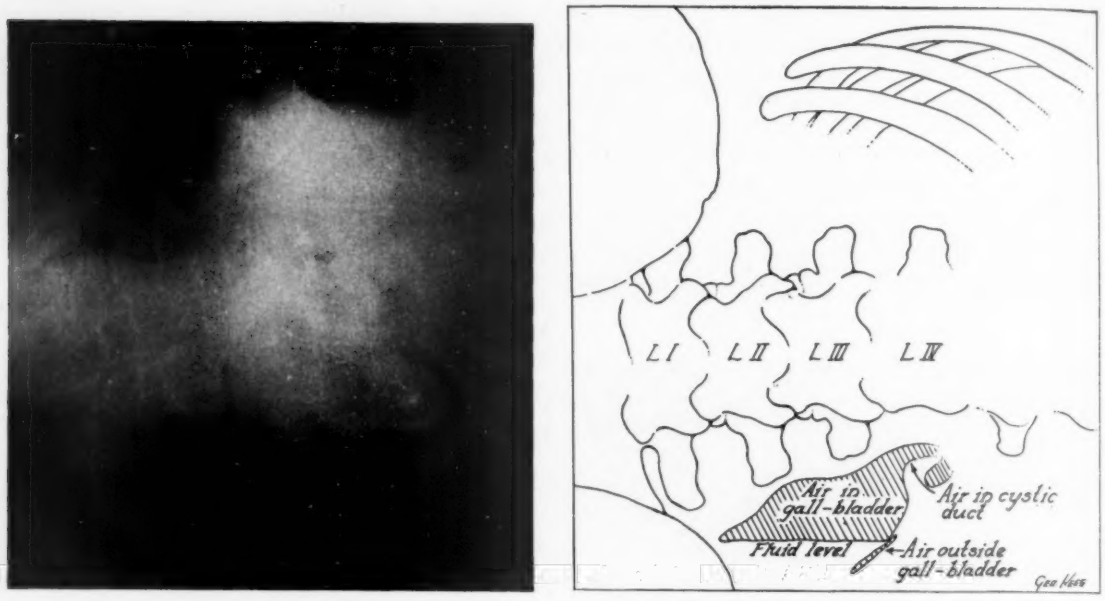

FIG. 6. Roentgenogram taken with the patient in right lateral decubitus.

healed per primum. His temperature dropped to normal approximately twenty-four hours following surgery. The remainder of his postoperative course was essentially uneventful and he was discharged on the tenth postoperative day.

When one considers the extensive nature of his disease, it is remarkable that this patient's postoperative course was so uneventful. Surgical drainage is the treatment of choice in cases of ruptured acute gaseous cholecystitis with abscess formation. The administration of polyvalent gas gangrene antitoxin is to be recommended but its effect is difficult to evaluate. This patient received no antitoxin.

Opinions are speculative as to how the organisms causing gallbladder disease actually reach the gallbladder. Rosenow[8] and Wilkie[12] support the theory and attempt to prove that the majority of these infections are blood-borne bacterial emboli which generally arise from streptococcal dental infections. The blood stream, lymphatics, biliary tree and abnormal communication of the gallbladder with the intestines have all been considered as possible routes of invasion. It is reasonable to assume, however, because of the proximity of the intestines and the frequent incidence of intestinal bacteria in the gallbladder that the intestinal tract is a common source of infection. This is especially true in cases of gaseous cholecystitis since the intestine is the normal habitat of the gas-forming bacteria and since blood-borne organisms should produce foci of gas infection in other parts of the body.

SUMMARY

Seventeen cases of acute gaseous cholecystitis reported in the literature are reviewed.

The clinical history and the roentgen findings of a case of acute gaseous cholecystitis with rupture of the gallbladder and abscess formation are described and illustrated.

Conservative treatment is recommended in uncomplicated acute gaseous cholecystitis.

We wish to thank Dr. E. A. Kindel for permission to publish this case.

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CYSTADENOMA OF THE PANCREAS

A REPORT OF TWO CASES SHOWING CALCIFICATION

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BENIGN cystadenomas of the pancreas, although relatively rare, are of sufficient importance to be considered in the roentgen differential diagnosis of space occupying upper abdominal lesions. Not only may fairly accurate localization be accomplished by roentgen examination but the true nature of the lesion may be suggested through correlation of the roentgen findings with the clinical signs and symptoms. The 2 cases herein reported are unusual in that both exhibited roentgenologically demonstrable calcification, a diagnostic point which has not been sufficiently emphasized in the literature.

CASE REPORTS

CASE 1. Mrs. I. Z. (Hosp. No. 3537), white housewife, aged fifty-three, was admitted to Deaconess Hospital on July 6, 1947, complaining of a mass in the upper abdomen, diarrhea and a 35–40 pound weight loss in the past four months. The symptoms began four months prior to admission when the patient first noted an increased number of soft yellow stools. There was no abdominal pain. It was at this time that she first became aware of a firm mass in the upper abdomen. The remainder of the history was non-contributory.

Physical examination revealed an elderly, undernourished, chronically ill female with a blood pressure of 125/74. The abnormal findings were confined to the abdomen. Here a large, round, smooth, non-tender, freely movable mass was outlined in the epigastrium. The mass did not move on respiration and appeared to be attached posteriorly. Bowel sounds were hyperactive. The liver could be palpated distinct from the mass.

Laboratory Findings. The sedimentation rate was 22 mm. in one hour. The red blood cell count was 4,800,000 with 13.5 gm. of hemoglobin. The white cell count was 10,200 and the differential count was normal.

Roentgen Findings. A roentgenogram of the abdomen taken July 7, 1947, in the recumbent position, disclosed a soft tissue mass in the right upper quadrant. In the upright position the mass shifted or fell to the right lower medial abdominal region overlying the fifth lumbar vertebra and upper sacrum. Rather dense radial calcification was noted in the mass.

FIG. 1. Case 1. Barium meal examination July 7, 1947, shows a calcified mass lying opposite the third and fourth lumbar vertebrae on the right side of the abdomen within the duodenal sweep. A radial calcific pattern is apparent. The duodenal curve is widened and the duodenum is stretched over the mass. There is no direct of invasion of the duodenal wall.

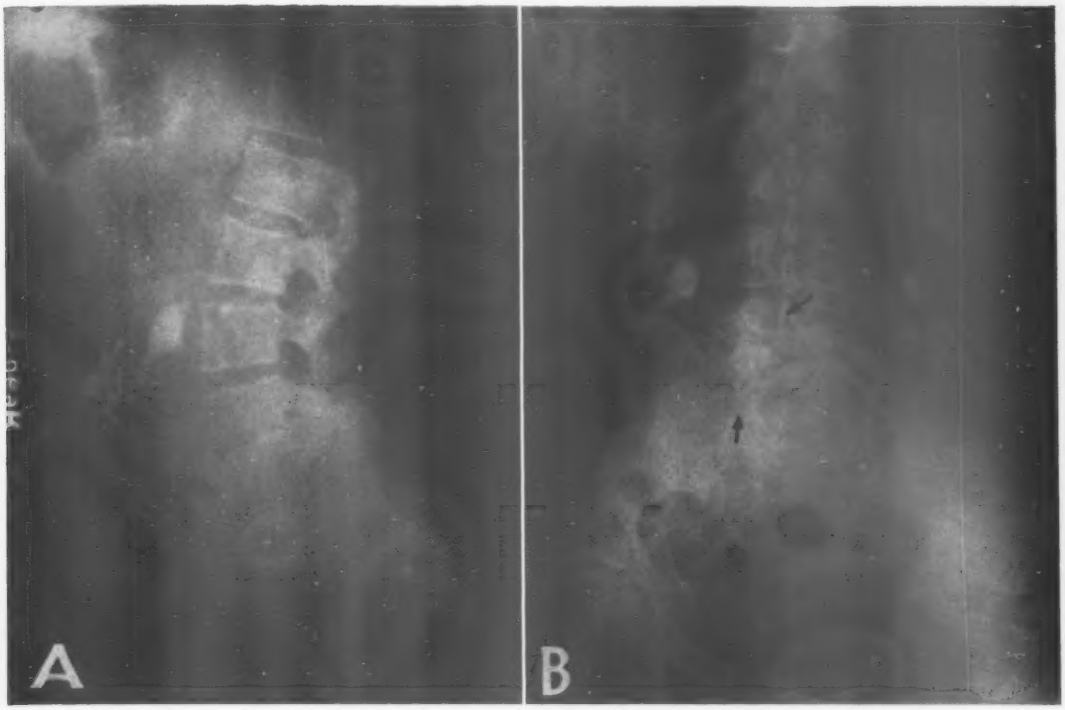

Fig. 2. Case 1. (*A*) Right lateral view of the abdomen during intravenous urography shows anterior position of the calcified mass and anterior displacement of the right kidney. (*B*) Upright roentgenogram during excretory urography demonstrates the downward and medial shift of the calcified mass to a point overlying the right side of the fifth lumbar vertebra and sacrum.

The opacified stomach antrum and pylorus were compressed by the mass occupying the region of the head of the pancreas (Fig. 1). The duodenal loop was widened and the duodenum was compressed on its inner aspect. The medial mucosal pattern of the second portion of the duodenum was distorted by extrinsic pressure but there was no actual destruction of the mucosal markings. The mass, thus outlined, measured approximately 9 to 10 cm.

Intravenous urography on July 8, 1947, showed the mass to be situated anteriorly in the abdomen but the right kidney appeared to be drawn downward and forward (Fig. 2*A*). There was a slight dilatation of the right upper urinary tract (Fig. 2*B*). The psoas border on the right side was rather faint. A roentgen diagnosis of a mass in the region of the head of the pancreas was advanced.

Hospital Course. The abdomen was opened under general anesthesia on July 9, 1947, and a large firm tumor was found replacing the head of the pancreas. The duodenum was stretched over one side. The tumor was removed along with the first and second portions of the duodenum. The pylorus was anastomosed to the third portion of the duodenum and the common bile duct to the stomach. An inadvertent nick in the portal vein was repaired. During surgery, the blood pressure fell progressively, and the pulse became rapid and weak. The patient left the operating room in a state of shock.

She was given plasma, fluids and one 500 cc. whole blood transfusion on the operating table. Following surgery, she received another 500 cc. transfusion and several stimulants. She, however, remained in shock and died at 4:25 A.M. July 10, 1947.

Examination of Surgical Specimen (S-889-47). The tumor was roughly rounded and measured 14 by 14 by 11 cm. Nineteen centimeters of duodenum was stretched over one side. The ampulla of Vater was identified and opened. Three centimeters of the common bile duct coursed over one surface of the tumor. The main pancreatic duct ended blindly after 2 cm. The intact external surface was composed entirely of

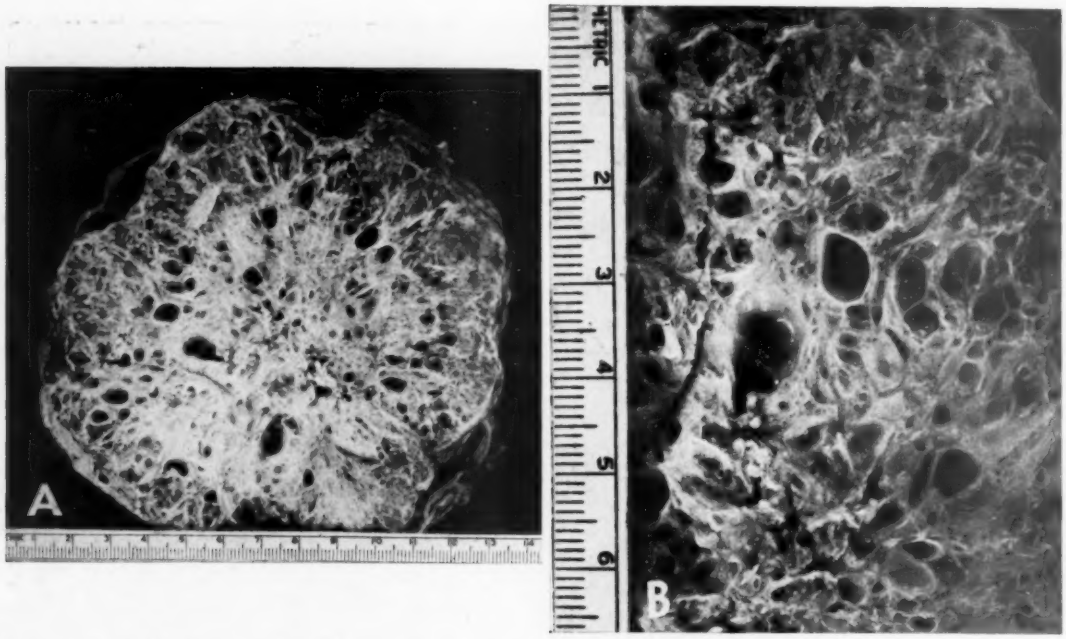

FIG. 3. Case 1. (*A*) Cross section of cystadenoma of the head of the pancreas showing stromal calcification. Note the radiating pattern of the trabeculae from a central nidus. (*B*) Close-up of the cut surface of the tumor demonstrating the "honeycomb" multicystic nature of the tumor.

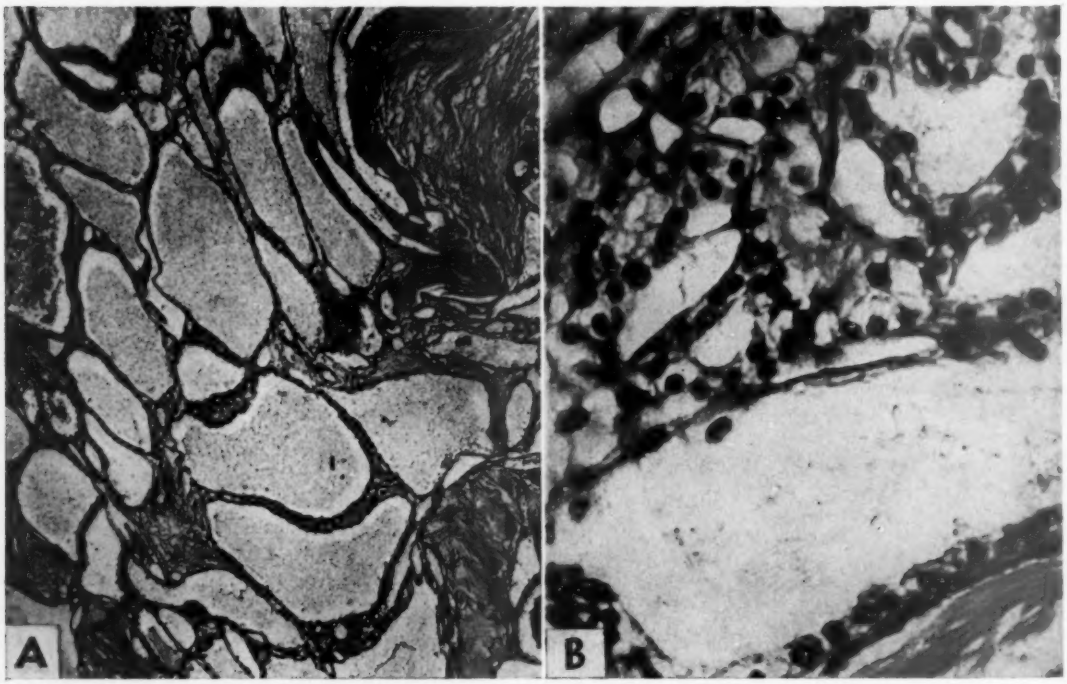

FIG. 4. Case 1. (*A*) Low power photomicrograph of pancreatic cystadenoma demonstrating the irregular variable-sized cysts containing finely granular material. The stromal trabeculae vary in thickness and some show hyalinization. Hematoxylin and eosin, ×50. (*B*) High power photomicrograph showing the cuboidal epithelium lining the smaller cystic spaces. Hematoxylin and eosin, ×500.

thin-walled cysts which ranged from 0.5 to 1.5 cm. in diameter. Some showed evidences of hemorrhage, others contained a clear lymph-like fluid. The tumor was sectioned with difficulty because of marked calcification of the stroma. The cut surface presented a honeycombed polycystic appearance (Fig. 3 *A* and *B*). Hyalinized and calcified stromal trabeculae radiated from an almost completely calcified central nidus.

Microscopically, the tumor was composed of variable-sized cystic spaces filled with homogeneous pale pink material (Fig. 4*A*). The lining epithelium was of a flattened endothelioid type, for the most part, but here and there small spaces could be found lined by definitely cuboidal cells (Fig. 4*B*). The stroma was variable in amount. In some places, it was hyalinized, in others calcified and, in a few places, of a loose areolar type. In the latter a scattering of lymphocytes was noted.

A roentgenogram of the surgical specimen showed a dense radial calcific pattern (Fig. 5).

Postmortem Examination (A-38-47). External examination revealed only an oblique right upper abdominal surgical wound closed by fourteen sutures and fine wire. Several rubber drains protruded from a stab wound to the right off the incision. Numerous vena puncture wounds were noted in the cubital fossae. The skin and mucous membranes were unusually pale.

Exploration of the abdomen revealed it to contain approximately 500 cc. of blood-tinged fluid. The drains were followed to the bed of the pancreas. The repaired portal vein was identified and found to be intact. The vein contained fluid blood. The anastomoses of the common bile duct and duodenum to the stomach were intact. A ligature surrounding the markedly dilated main pancreatic duct was found to encircle and completely occlude the superior mesenteric artery which arose anomalously from the celiac axis. The entire small intestine, the cecum and the ascending and transverse colon were dilated, edematous and showed a dark green and purplish-red discoloration. The tumor bed was clean and dry.

Approximately 10 cm. of the body and tail of the pancreas remained in the body. This was composed of only a small amount of fibrous pancreatic tissue surrounding the markedly dilated main pancreatic duct. The duct at the point of ligature measured 4 cm. in circumference.

Fig. 5. Case 1. Roentgenogram of cystadenoma of head of pancreas shows dense radial calcification—a "sun-burst" appearance. A metallic pointer, 5.4 cm. in length, indicates the central calcified nidus.

The spleen and liver were without significant gross changes. The gallbladder showed a moderate degree of cholesterolosis.

The kidneys were somewhat larger than usual weighing 170 and 165 grams respectively. The capsules stripped easily, revealing relatively smooth, pale, slightly mottled surfaces. The kidneys were flabby and of a softer consistency than usual. On section, the cortices were swollen and pale; the medullae showed increased tan-brown streaking.

The renal pelves, ureters and urinary bladder were unchanged. Examination of the internal genitalia revealed only slight granularity of the cervical epithelium surrounding the os.

Examination of the thoracic organs revealed a few fibrous pleural bands and dependent pulmonary congestion. The heart weighed 345 grams. The myocardium was firm but pale. The valves were normal except for several flat athermatous plaques on the aortic aspect of the anterior mitral cusp. The coronary arteries were smooth and elastic throughout. The aorta and its major branches were unchanged.

The contents of the skull were not examined.

FIG. 6. Case II. Excretory urography (July 18, 1947) shows a large mass on left side of abdomen producing upward and medial displacement of the left kidney, partial obstruction of the left ureter, right lateral lumbar scoliosis and partial obliteration of the left psoas muscle shadow. Irregular calcific deposits are apparent within the mass. The changes in the proximal left femur are characteristic of Paget's disease.

The significant microscopic changes were confined to the pancreas and kidney. Sections of the pancreas revealed almost complete atrophy of the exocrine tissue and replacement by fibrous tissue sparsely scattered with chronic inflammatory cells. The pancreatic ducts were dilated and lined by flattened atrophic epithelium. The islets of Langerhans, on the other hand, were normal in size and structure.They were set in a fibrous and fatty stroma which contained virtually no acinar structures.

Sections of the kidneys revealed markedly swollen glomeruli which, however, showed no basement membrane thickening or cellular infiltration. The glomerular capsules were uniformly thin. The epithelium of the proximal convoluted tubules was swollen and coarsely granular. The lumina contained considerable pink granular debris. A similar but less marked change was apparent in the distal convoluted tubules. Both limbs of Henle's loop and the collecting tubules were unchanged.

The summarized anatomical diagnosis was: (1) Status following excision of calcified cystadenoma of the head of the pancreas, partial duodenectomy, duodenogastrostomy and choledochogastrostomy; (2) obstructive dilatation of the main pancreatic duct with atrophy and fibrosis of the pancreas; (3) ligation of anomalous superior mesenteric artery; (4) early gangrene of small intestine and proximal two-thirds of the colon; (5) renal lesion of shock.

CASE II. Mrs. E. G. (Hosp. No. 3781), aged seventy-five, entered Deaconess Hospital on July 17, 1947, with complaints of loss of appetite, nausea, vomiting, and diarrhea for a period of about two weeks. She had noticed a mass in the upper abdomen for ten to fifteen years and admitted that she has been suffering with episodes of "gas," nausea, vomiting and attacks of indigestion for the past several years. She had previously been treated for "gallbladder trouble." Approximately two weeks before admission to the hospital, the patient experienced an episode of indigestion and "intestinal flu." The character of the stool or vomitus was not known, but she had been treated for "anemia" for at least one year. The history by systems was essentially negative.

Physical examination revealed a well preserved elderly white female, who did not appear acutely ill, but was partially deaf. The blood pressure was 150/65. The pulse was 80 per minute and regular. Examination of the head, neck and chest was essentially normal. The abdomen was protuberant but soft. No scars were present. A large, firm, somewhat irregular, slightly tender mass was found in the left upper abdomen. It moved slightly with respiration. The mass extended obliquely downward and to the right to a point 2 inches beyond the umbilicus. The liver and kidneys were not palpable.

Laboratory Findings. Urinalysis showed no abnormality. The specific gravity was 1.010. The blood findings were also essentially negative. The white blood cell count was 12,300. The differential was normal.

Roentgen Findings. Roentgen examination of the abdomen on July 18, 1947, disclosed a large soft tissue mass measuring approximately 10 by 15 cm. on the left side of the abdomen, extending from the level of first lumbar intervertebral disc to the lumbosacral joint. This mass contained numerous calcific spicules and fragments. The left kidney shadow was pushed upward

toward the diaphragm (Fig. 6). The lower portion of the left psoas shadow was ill defined. The lumbar spine was curved toward the right. No metastasis was seen in the bones but changes in the proximal left femur are indicative of Paget's disease.

Barium meal studies showed anterior displacement of the lower portion of the stomach (Fig. 7*A*). The stomach was also pushed toward the right and there was some irregularity of the greater curvature (Fig. 7*B*). The duodenal sweep was compressed or narrowed due to pressure from the left.

Barium enema studies revealed downward and anterior displacement of the distal transverse colon and anterior and lateral displacement of the splenic flexure. The mucosal pattern of these segments was not destroyed.

Excretory urography showed upward displacement of the left kidney (Fig. 6). This kidney appeared to be slightly larger than the right, but rotation was believed to be responsible for the apparent asymmetry. The lower pole of the left kidney was situated at the level of the second lumbar vertebra. There was partial compression of the middle third of the left ureter and lack of filling of the distal third. The lateral view disclosed no additional information. In the upright position some dye was retained in the upper left ureter and there was slight dilatation. The roentgen observations permitted a diagnosis of a retroperitoneal tumor, probably in the tail of the pancreas.

Hospital Course. On July 23, 1947, a laparotomy was performed under general anesthesia. The pancreas was approached through the gastrocolic omentum. A large multicystic tumor mass was identified occupying the entire tail of the pancreas. This measured approximately 8 by 12 cm. It was surrounded by large veins and was adherent to the surrounding organs. Because of the extensive blood supply, the mass was not deemed resectable and only a small fragment of tissue was removed for microscopic examination.

The patient made an uneventful recovery

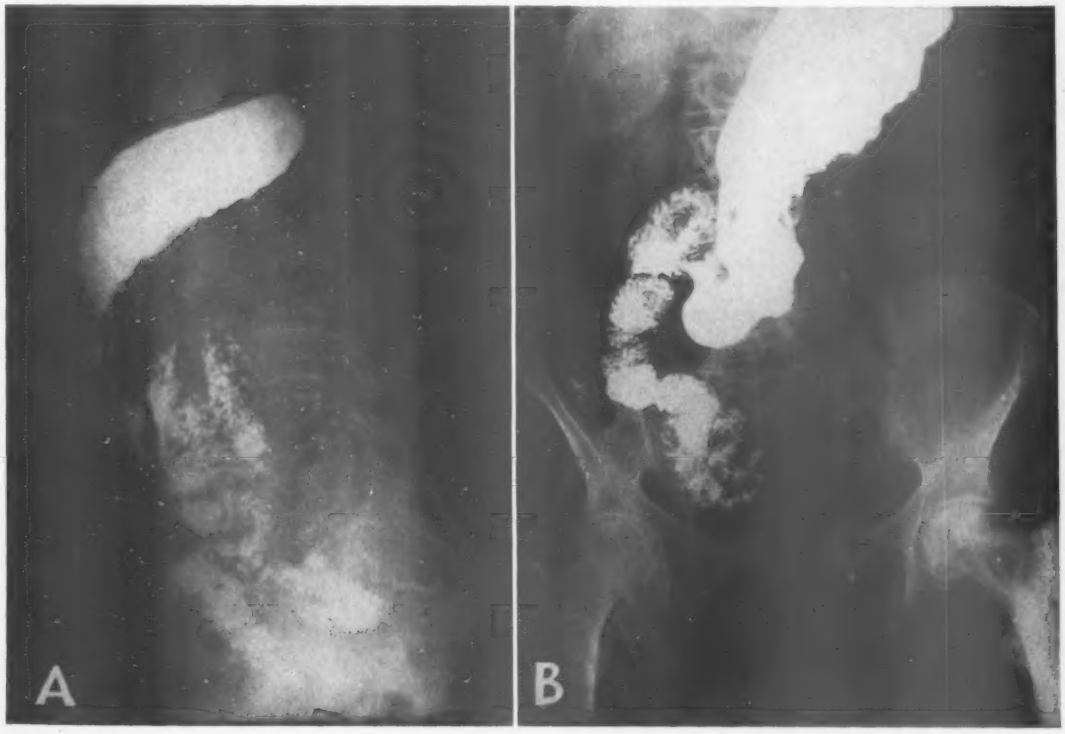

Fig. 7. Case 11. (*A*) Left lateral view during barium meal examination shows anterior displacement of the stomach by a large mass in the region of the tail of the pancreas. (*B*) Opacification of upper gastrointestinal tract shows displacement of the stomach and duodenum to the right by a mass which appears to be intimately associated with the greater curvature of the stomach. The greater curvature displays a ragged outline. The duodenal sweep is compressed as a result of extrinsic pressure from the left.

and was discharged on August 1, 1947, eight days postoperatively.

Subsequent Course. A course of deep roentgen therapy was administered during the period between July 30 and September 13, 1947. Two 10 by 15 cm. anterior oblique fields, each tilting toward the center of the mass, were employed. A total of 2,000 roentgens, measured in air, was delivered to each of these areas. The pain and discomfort which were present for at least one month prior to surgery disappeared following roentgen therapy.

Follow-up roentgen studies of the abdomen in November, 1947, and February, 1948, disclosed no essential change in the size or shape of the soft tissue mass or in the density, size, configuration or spacing of the soft tissue calcifications.

Examination of Surgical Specimen (S-975-47). The specimen consisted of a tiny fragment of tan-brown tissue which measured only 1.5 by 0.5 by 0.4 cm. On section, it appeared to be composed of numerous tiny cysts separated by tan fibrous tissue. The outer surface was smooth.

Microscopically, the fragment was composed of numerous, variable-sized cystic spaces lined by cuboidal epithelium which in many places was flattened and resembled endothelium (Fig. 8*A*). In the majority of the smaller spaces, the epithelial cells were definitely of a cuboidal type showing a small amount of clear cytoplasm and small, round, dark, basal placed nuclei (Fig. 8*B*). The spaces were filled with homogeneous, pale pink amorphous material. A few contained extravasated red blood cells. The spaces were separated by trabeculae of hyalinized connective tissue which varied markedly in thickness. Focal scatterings of chronic inflammatory cells were found in the trabeculae. Diagnosis: Cystadenoma of pancreas.

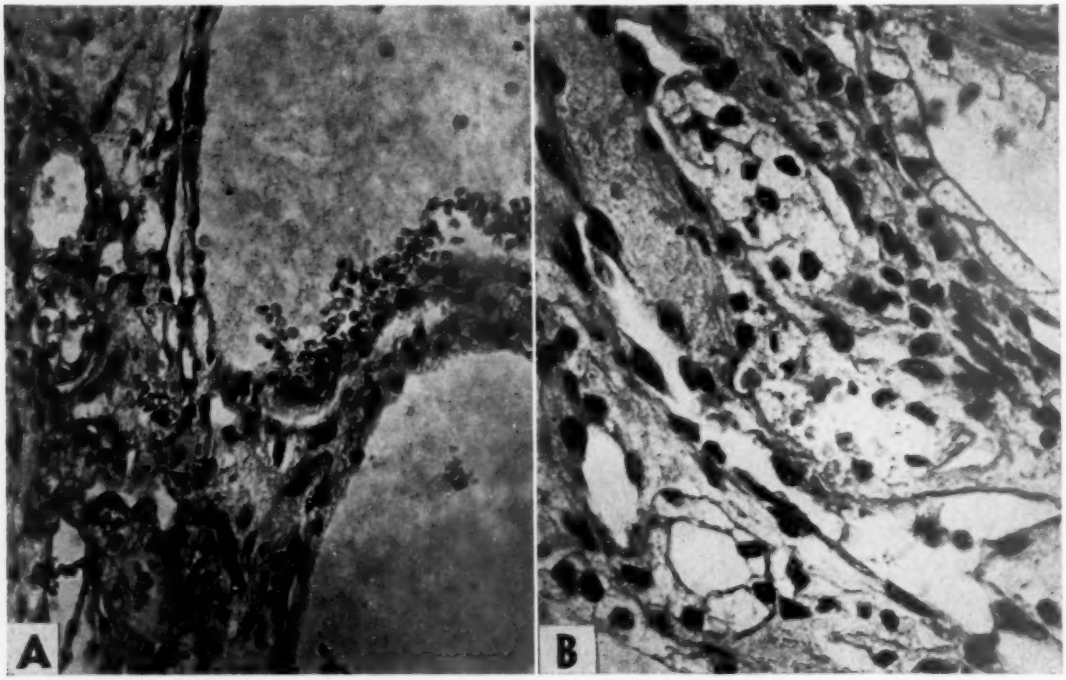

FIG. 8. Case 11. (*A*) Photomicrograph of cystadenoma of the tail of the pancreas. Note the variable-sized cysts containing finely granular material and a few extravasated erythrocytes. Hematoxylin and eosin, ×400. (*B*) High power photomicrograph showing the clear cuboidal epithelium lining the small cystic spaces. Hematoxylin and eosin, ×700.

DISCUSSION

The true incidence of cystadenoma of the pancreas is not known and cannot be determined because many cases are buried in reports on pancreatic surgery, hidden in discussions of wholly unrelated non-

neoplastic pancreatic cysts or reported under a variety of erroneous diagnoses. Brunschwig[4] estimated that about 50 reports had appeared in the literature up to 1942, including the 37 cases compiled by Yamane from the literature up to 1921. Eleven additional cases are to be found in the available literature since 1942.[1,2,3,7,11,12] The majority of these reports are lacking in pathologic detail. The case report and review of the literature published by Jemerin and Samuels,[7] however, is most complete. The 2 cases herein presented would bring the total recorded cases to about 63.

Cystadenoma of the pancreas is almost exclusively a tumor of the female; only 11 per cent of the recorded cases have occurred in males.[2] The average age at the time of diagnosis is forty-eight years, the extremes ranging between seventeen and seventy-six years of age.[2] It would appear, however, that the onset of tumor growth occurs at a considerable time before diagnosis since the tumors usually present the histopathologic picture of relatively slow growth and the majority of patients give a suggestive symptomatic history of one to ten years' duration.

The etiology of pancreatic cystadenoma is unknown. Bowers, Lord and McSwain[3] comment on an association with gallbladder disease in 4 out of their 5 cases but question any pathogenic relationship between the two. Similarly it is doubtful if a causative relationship can be assumed between the occurrence of diabetes and this tumor. Although diabetes was present in 21 per cent of the cases of cystadenoma reviewed by Benson and Gordon,[2] it was in no way affected by surgical extirpation of the tumor. Carling and Hicks[5] reported a case in which the diabetes was much more severe following operation. Bowers *et al.*[3], on the other hand, reported improvement postoperatively in 1 of their 3 diabetic patients.

Pathology. Although pancreatic cystadenoma is a definite pathologic entity, little is known of its histogenesis. The true position of the tumor in relation to other diseases of the pancreas has been confused by many authors who attempt to classify it among the unrelated non-neoplastic pancreatic cysts or who attempt to relate this obvious neoplasm to fibrocystic disease of the pancreas or of other organs.[5] There are three principal theories of origin: (1) displaced embryonic cells, from the alimentary canal primardia, the urogenital fold or the mesonephros, (2) neoplastic proliferation of the pancreatic acinar epithelium, and (3) proliferation of the cylindrical pancreatic duct epithelium. None of the theories is entirely satisfactory but the latter two would appear most likely. If the embryonic theory were true one would expect to find similar tumors elsewhere in the abdomen or retroperitoneal tissues. This is not the case. Cystadenomas of the type herein reported are distinctive and, to our knowledge, found only in the pancreas. On the other hand, it is probable that both pancreatic acini and ducts give rise to cystic neoplasms. The cystadenomas reported in the literature on critical analysis will be found to fall into two groups, the softer, more cellular, papillary cystadenomas displaying cylindrical epithelium, presumably arising from the large pancreatic ducts, and the tumors of the type herein reported lined by endothelioid cuboidal epithelium which probably arise from the pancreatic acini or small ducts.

Pancreatic cystadenomas have a fairly characteristic gross appearance. Although covered by a thin fibrous capsule, the external surface is irregular, presenting a polycystic surface which has been likened to a bunch of grapes. The tumors are most commonly situated in the tail or body of the pancreas,[2,4] but are occasionally encountered in the head. They vary considerably in size but in most instances range between 2 and 8 cm. in diameter. Tumors measuring 14 cm. in diameter have been reported by Whipple and by Dragstedt[4] and one measuring 15 cm. and weighing 2,050 grams was described by

Kennard.[8] The tumor almost invariably is surrounded by widely dilated veins, presumably due to local pressure as well as to the nutritional requirements of the tumor. This was prominent in both of our cases. Vascularity was so extensive in Case II that the surgeon deemed the tumor inoperable. Depending upon the size and location of the tumor, there may or may not be considerable distortion and/or displacement of the surrounding viscera. The tumors situated in the head of the pancreas may cause partial or complete occlusion of the common bile duct and occlusion or complete obliteration of the pancreatic duct. This is well demonstrated in our Case I in which the main pancreatic duct was lost in the tumor mass and the remaining pancreatic tissue in the body and tail showed almost complete atrophy of exocrine elements.

The cut surface of these tumors, too, is characteristic and the polycystic configuration is perhaps best demonstrated here. The cysts range from microscopic dimensions to 1 or 2 cm. in diameter, imparting a porous or honeycomb appearance to the surface. They ordinarily contain a clear lymph-like fluid but on occasion the content has been described as mucoid[12] or sanguineous. The supporting stroma is variable in amount but is commonly abundant, especially in the center of the mass. It appears to radiate from this central nidus in a sun-burst-like manner. The radiating stromal trabeculae may be rather wide, are commonly firm and hyalinized and frequently contain spicules of calcified material. Stromal calcification has been frequently alluded to in the literature,[3,5,4,7] but apparently insufficiently emphasized since heretofore it has not been demonstrated clinically by roentgenograms.

Occasional tumors are less markedly cystic, grossly presenting a softer more cellular yellowish-gray cut surface. These are the papillary cystadenomas in which the microscopically demonstrable cysts are filled with irregular papillary masses covered by tall columnar epithelium. They give rise to the rare papillary cystadenocarcinomas of the pancreas and may present a difficult histopathologic differential diagnostic problem. In the more usual microscopic picture, demonstrated by both of our cases, the cysts are lined by a single layer of low cuboidal epithelium supported by a moderate amount of hyalinized or partially calcified stroma. The epithelium in some tumors is so flattened as to resemble vascular endothelium. This together with the scattering of lymphocytes frequently seen in the looser portions of the stroma may give one the impression of a vascular tumor, a lymphangioma or angio-endothelial sarcoma. A number of cases so misdiagnosed are to be found in the literature.[4,6] Our Case I is a tumor of this type. It was interpreted as a lymphangioma on the initial tissue preparations but further sections revealed definitely cuboidal type epithelium and the true nature of the tumor.

Cystadenomas of the pancreas, whether papillary or non-papillary, are benign tumors growing slowly by expansion. Although several examples of carcinoma arising in a pre-existing cystadenoma have been reported,[8] this occurrence is extremely rare and the majority of the so-called "malignant cysts" are probably malignant from their inception. Local recurrence may be expected, however, if the tumor is incompletely removed or improperly treated by marsupialization.

Roentgen Aspects. The roentgen features of pancreatic tumors depend on the site of origin (head, body or tail) and the direction of growth. Localization of a soft tissue mass to the region of the pancreas is possible by ascertaining the relationship of the mass to surrounding structures; i.e., colon, stomach, duodenum, kidneys, psoas muscles, ureters, but determination of the type of tumor present is not always possible.

Unfortunately, an excretory method of visualizing the pancreas or pancreatic ducts is not available. In spite of this, pancreatic tumors may frequently be visualized on roentgenograms. Poppel and Marshak[11]

list such direct signs as dense masses, calcifications, opaque foreign bodies and collections of gas and fluid levels in upright or lateral recumbent views. It is important to note that pancreatic tumors, although retroperitoneal in origin, not infrequently present clinical and roentgen characteristics of an anterior abdominal tumor.

Poppel and Marshak[10] comprehensively consider the indirect signs of pancreatic tumors, signs limited to the contrast-filled stomach or intestine. In our 2 cases, although gastrointestinal changes were prominent, alterations were also discernible in the urinary tract which afforded additional localizing data. It is unlikely that these signs are specific and only observed in cystadenomas of the pancreas. On the other hand, we feel that they are of sufficient importance to be added to the list of indirect signs of pancreatic tumors.[10] The augmented list of signs would then appear as follows:

I. *Head of the pancreas.*

(a) Widening or spreading out of the duodenal loop or widening of the semicircular arc described by the duodenum. The larger, smooth, rounded defects are usually due to cysts. Extrinsic pressure alters the direction of mesial ends of the duodenal mucosal folds (valvulae conniventes).
(b) Displacement of the duodenal loop toward the right and anteriorly; the stomach may be displaced upward and forward.
(c) Fixation of the duodenal loop, especially the medial wall.
(d) Diminished diameter of the duodenum, causing obstruction and delay in emptying of the stomach.
(e) Irregularity of contour of the inner concave border of the descending duodenum with or without alteration or destruction of mucosal pattern. Destructive changes most likely due to carcinoma.
(f) Alteration of duodenal peristalsis. Diminished, absent or antiperistalsis.
(g) Palpable mass.
(h) Downward and forward displacement of the transverse colon.
(i) Extrinsic defect in outer wall of the descending duodenum in cases of common duct obstruction.
(j) Central filling defect in the duodenal bulb due to a pancreatic nodule impinging on the lumen of the duodenum from behind (Kirklin).
(k) Cholangiography.
(l) Signs of acute inflammation.
(m) Alteration of right psoas muscle shadow (Case 1, Fig. 1).
(n) Downward and anterior displacement of right kidney (Case 1, Fig. 2*A*).

II. *Mass in body or tail of pancreas.*

(a) Stomach displaced and indented forward, upward or downward causing compression and obstruction.
(b) Mid-transverse colon is displaced forward and downward.
(c) Ascending duodenum and duodenojejunal flexure displaced and indented in a forward, downward or upward direction causing compression and obstruction. The more proximal duodenum may be dilated.
(d) Alteration of left psoas shadow (Case II, Fig. 6).
(e) Upward displacement of left kidney (Case II, Fig. 6).
(f) Compression of ureter causing partial obstruction (Case II, Fig. 6).

It is seldom possible to make an early roentgen diagnosis of carcinoma of the pancreas. There are several reasons for failure. Before symptoms of any appreciable severity appear, the lesion is most often inoperable. The clinical signs and symptoms are not recognized early in the course of the disease, either by the patient or the physician, and the diagnosis is not made until painless jaundice, or diarrhea develop. Not all pancreatic tumors, however, are malignant. It is in the diagnosis of the benign lesions that roentgen examination can be of greatest help.

In both of our cases, the roentgenograms showed rather striking calcification of the tumor. In the tumor situated in the head of the pancreas (Case 1), the calcific deposits

were arranged in a radiating "sun-burst" pattern about a central completely calcified nidus. This was easily demonstrable on the preoperative roentgenogram (Fig. 1) and was confirmed by a film of the surgical specimen (Fig. 5), and the appearance of the cut surface of the tumor (Fig. 3*A*). The calcification in our second case was less marked and without as orderly a pattern. It was, nevertheless, clearly visible on the roentgenograms. Here the calcium occurred in small irregular particles scattered haphazardly throughout the tumor (Fig. 6 and 7*B*).

Although stromal calcification of pancreatic cystadenomas has been noted by others in the pathological examination of the extirpated tumors, it has not to our knowledge been demonstrated roentgenologically. It is indeed strange that tumors identical to ours in other respects, such as Brunschwig's[4] Case No. 267931 and Case 1 reported by Carling and Hicks,[5] showed no roentgen evidence of calcification when it was prominent on pathological examination.

The dissimilar patterns of calcification in our 2 cases are perhaps deserving of additional comment. It will be noted that in Case 1 and in other reported cystadenomas occurring in the head of the pancreas,[4,5] the calcification appeared in a radial "sun-burst" pattern. On the other hand, the calcific deposits in the tumors located in the tail or body of the pancreas[3,4,7] occurred in a more or less haphazard irregular fashion. This is well demonstrated by our second case. The reasons for these two different calcification patterns are not apparent. One might speculate that variations in blood supply or perhaps the restraining influence of surrounding structures play a part. Be that as it may, we believe that these patterns are of importance clinically in that they may foretell the true nature of a pancreatic lesion preoperatively as well as assist in its localization.

The enlarged pancreas by virtue of its retroperitoneal location may encroach upon the urinary tract or psoas muscles. Masses in the head of the pancreas are capable of causing alteration of the roentgen shadows of the psoas muscle on the right side, right kidney and ureter. In Case 1 excretory urography demonstrated downward and anterior displacement of the right kidney. Poppel[9] offers the following explanations for this finding:

> That a tumor of the head of the pancreas growing towards the right would displace the descending duodenum further towards the right and pre-empt the anterior space of the right kidney. Later the tumor may attach itself to this surface and pull the kidney forward when the pancreas becomes more rigid and straight due to the tumorous infiltration. That originally the unciform process of the head of the pancreas was uncoiled and had originally slipped between the duodenum and kidney, forming an incomplete annular pancreas. Should tumor supervene, it might attach itself to the kidney and yank it forward. On the other hand, the unciform process may originally have been behind the right kidney. Then, of course, the explanation of anterior displacement of the kidney is easily understood.

Neither the surgeon nor pathologist found excessive pancreatic tissue or an incomplete annular pancreas. The first explanation of Poppel, therefore, seems the most plausible.

Tumefaction of the tail of pancreas can give rise to abnormalities in the left upper urinary tract. The left kidney of our second patient (Fig. 6) is displaced upward and the ureter is compressed. The latter is responsible for slight obstructive hydronephrosis. The psoas muscle shadow is modified by the large retroperitoneal mass. The finding of Paget's disease in the left femur probably represents a mere coincidence.

Roentgen Therapy. To the best of our knowledge, deep roentgen therapy has not previously been employed in the treatment of cystadenoma of the pancreas. In the patient with the inoperable tumor of the tail of the pancreas, roentgen therapy was administered empirically. Anterior portals

were employed because the mass presented anteriorly. Follow-up roentgen studies a few months later failed to show any appreciable change in the size, configuration or number of calcifications and the mass was approximately of the same size as prior to roentgen therapy. There was, however, less local tenderness, and the patient subjectively was markedly improved. This was probably due to the roentgen effects on the surrounding inflammatory reaction. It is perhaps somewhat premature to suggest that roentgen therapy might have some inhibiting influence on the further growth of such tumors. We do not believe that further deep roentgen therapy is indicated because of the advanced age of the patient and since it would appear unlikely that she will succumb to her pancreatic disease. The previous clinical signs of pancreatic insufficiency also disappeared following therapy but this, in all probability, is due to more careful dietary management.

These results are obviously inconclusive. An evaluation of the efficacy of deep roentgen therapy in the treatment of pancreatic cystadenomas must await further experience.

CONCLUSIONS

Two proved cases of benign pancreatic cystadenoma showing calcification are reported. These cases are unique in the literature in that the calcium deposits within the tumors were demonstrated clinically by means of roentgenograms. The significance of this feature is discussed.

The pathologic features of pancreatic cystadenomas are reviewed. The compilation of roentgen signs of pancreatic neoplasms of Poppel and Marshak is reviewed and augmented by the addition of renal and psoas changes exemplified in the presented cases. The mechanisms of these changes are discussed.

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CALCIFICATION IN RETROPERITONEAL NEUROBLASTOMA*

REPORT OF THREE CASES WITH TUBERCULOID REACTION IN ONE CASE

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ALTHOUGH calcification occurs not infrequently in neuroblastoma, its roentgenologic detection is uncommon. In a review of the literature, covering over one hundred articles, published from 1901 to 1946, we found only 18 cases[1,3,4,6,9,10,11,13,14,15] of neuroblastoma in which calcification was noted in the roentgenograms. We report 3 additional cases, seen in the last eighteen months, of pathologically verified neuroblastoma with calcification demonstrated by the roentgenologist.

REPORT OF CASES

CASE I. V. H., a colored girl, aged fifteen months, was admitted to the Edward J. Meyer Memorial Hospital on January 17, 1946, for swelling of the abdomen and limp of the right leg of one month's duration.

Physical examination revealed a firm, nodular, non-movable mass in the left side of the abdomen extending to the mid-epigastrium.

In a roentgenogram of the abdomen, the roentgenologist reported: "Just beneath the eleventh rib above the kidney, are several small, calcified densities suggesting a possible pathologic lesion in the suprarenal gland."

At operation on January 21, 1946, a large, lobulated retroperitoneal mass filled the entire left side of the abdomen and extended across the midline. The left kidney was not identified. The mass was considered inoperable because of local invasion, and on biopsy it was proved microscopically to be "a malignant tumor of the neuroblastoma group with focal calcification."

The patient received a course of roentgen therapy, 1,950 r to the left anterior portion of the abdomen and a similar amount to the left posterior portion of the abdomen over a twelve day period. Treatment was stopped because of a decrease in the leukocyte count. On August 9, 1946, no abdominal tumor was palpable on physical examination. Follow-up roentgen studies at this time again demonstrated small calcified densities which had not changed from those in the previous examination. Films of the skull revealed slight generalized mottling over the vertex and in the frontal bone. At laparotomy on September 14, 1946, no single tumor was seen in the abdomen; there were scattered bilaterally, throughout the retroperitoneal region, numerous hard nodules averaging 1–2 cm. in diameter. One of these was excised and microscopically showed extensive necrosis with calcification and fibrosis. In the periphery, neuroblastoma was preserved.

In July, 1947, enlarged, cervical lymph nodes appeared. Pertinent laboratory findings at this time included: Blood calcium 12.4 mg. per 100 cc.; blood phosphate 8 mg. per 100 cc.; alkaline phosphatase 2 units. Biopsy of a cervical lymph node disclosed metastatic neuroblastoma with necrosis, focal calcification, and tuberculoid reaction.

The patient was given a course of nitrogen mustard therapy, 1.4 mg. intravenously four times on alternate days without any apparent improvement. Subsequently, the patient's condition became rapidly retrogressive, with development of generalized osseous metastases, bilateral exophthalmos, and marked progression of cervical metastases. Death occurred on January 6, 1948. The final diagnosis at autopsy was: Status following biopsy of retroperitoneal neuroblastoma and metastatic neuroblastoma; retroperitoneal atypical ganglioneuroma (measuring 11 by 6 cm.) of left side of abdomen originating in the left adrenal gland with focal calcification; metastatic neuroblastoma in right adrenal gland, liver, skull, ribs, cervical, paravertebral, mediastinal and inguinal lymph nodes; marked anemia; fatty degeneration of

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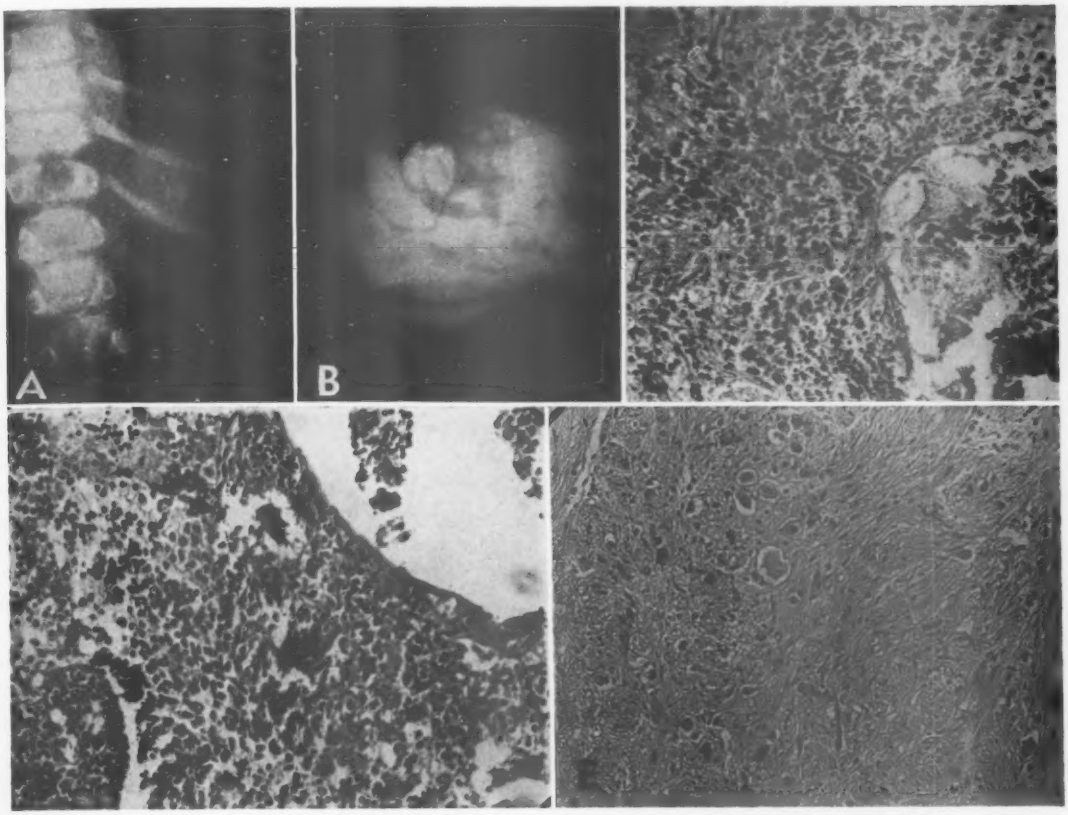

Fig. 1. (*A*) Roentgenogram of abdomen with focal calcification between left eleventh and twelfth ribs. (*B*) Roentgenogram of abdominal organs postmortem with focal calcification in right upper area. (*C*) Neuroblastoma (first biopsy) with focal calcification in right lower corner. (*D*) Tuberculoid reaction in metastatic node with Langhans type giant cell. (*E*) Ganglioneuroma; postmortem specimen.

myocardium with enlargement of heart; hyperemia and edema of the lungs; so-called congenital absence of right coronary artery.

Case II. W. L., male, white, aged ten, was admitted to the Buffalo Children's Hospital on April 8, 1946, with a history of pain in the lower back, anorexia, and listlessness for five months.

On physical examination, a mass was palpated in the left flank.

On roentgen study of the abdomen, the roentgenologist reported diffuse, calcific densities in the left side of the abdomen, extending from the tenth dorsal vertebra downward along the left side to the fourth lumbar vertebra. The densities were apparently in a mass which had pushed the left kidney downward and to the side. On laparotomy, a large, retroperitoneal tumor was found and deemed inoperable. Biopsy, apparently taken from the capsule of the node, revealed only fibrous and fatty tissue. The clinical impression, however, was "malignant tumor" (? Wilms', or ? neuroblastoma).

On September 16, 1946, the patient complained of lumbar backache which had been getting worse. At operation, a retroperitoneal mass was found extending from the dome of the left hemidiaphragm down to the umbilicolumbar region. The spleen appeared about four times its normal size. The splenic flexure of the colon was directly over the tumor mass and was separated from the mass through a lateral incision. The mass lay above the left kidney and there was a question whether it had originated in the kidney. About two-thirds of the mass was mobilized but lymph nodes around the aorta were so involved that they prevented a complete removal of the tumor and metastases. From biopsy of a node, located directly over the aorta, the pathologic report concluded: "Apparently the bulk of the tumor tissue is undifferentiated embryonal mesonephric blastoma."

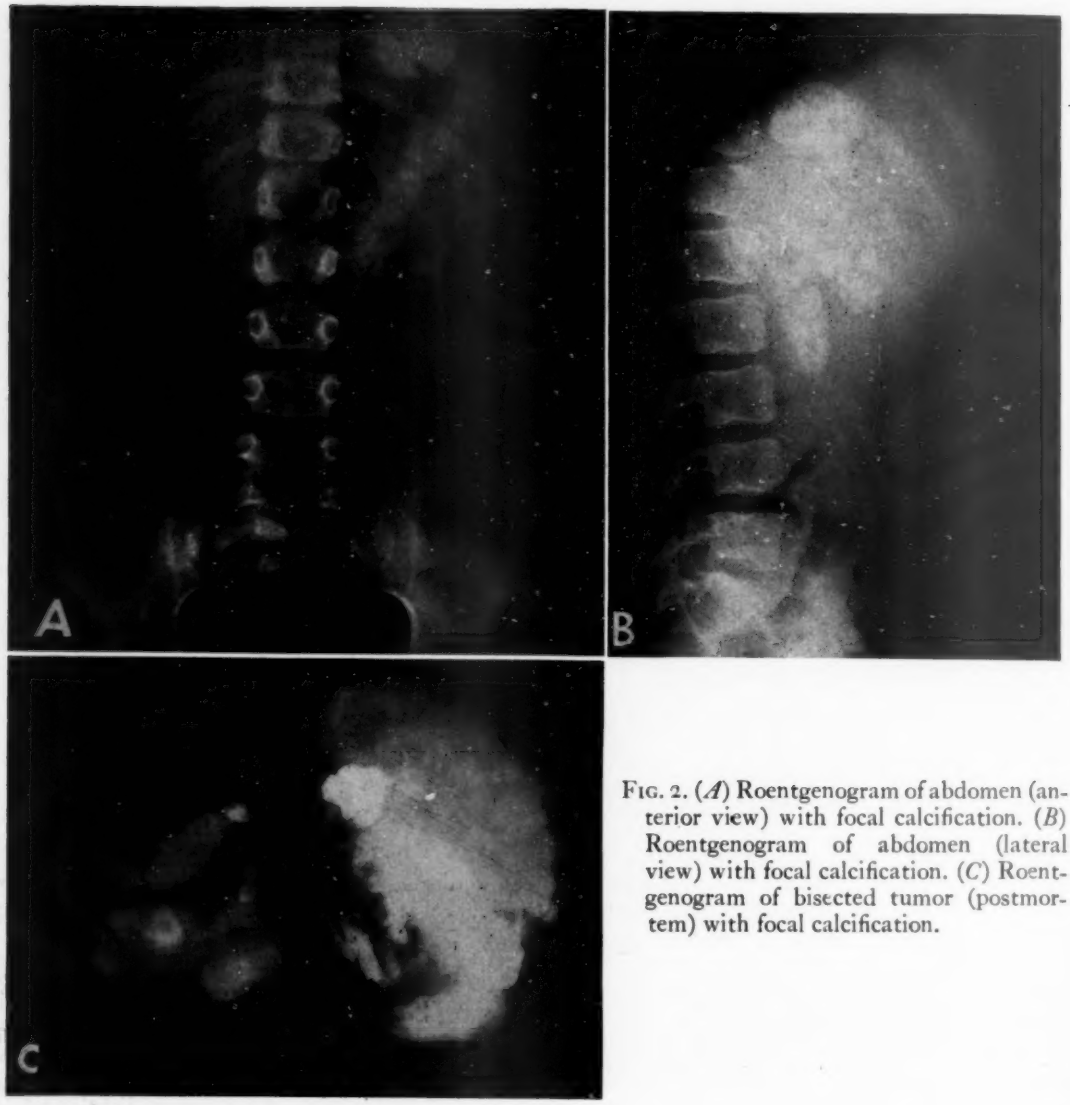

FIG. 2. (*A*) Roentgenogram of abdomen (anterior view) with focal calcification. (*B*) Roentgenogram of abdomen (lateral view) with focal calcification. (*C*) Roentgenogram of bisected tumor (postmortem) with focal calcification.

The roentgenologist, however, on the basis of calcification, changed his diagnosis of Wilms' tumor. Postoperative roentgen therapy, 2,500 r over the anterior abdomen and a similar amount over the posterior abdomen was given in divided doses, varying from 100–200 r without definite improvement.

On September 8, 1947, the patient was admitted to the Edward J. Meyer Memorial Hospital with an abdominal mass on the left side extending from the costal margin to the iliac crest. Preliminary roentgenogram of the abdomen showed a homogeneous density overlying all of the abdomen, with several large, irregular masses of calcified density in the left upper quadrant. In roentgenograms of the femurs, several areas of decreased density surrounded by slight bony reaction were seen in both femoral necks. The patient died at home on October 12, 1947.

The final diagnosis at autopsy was: Huge (28 by 18 cm.) nodular neuroblastoma of the left retroperitoneum extending from the diaphragm to the pelvis with regressive changes and calcification invading and displacing and compressing abdominal structures including the left kidney and ureter, spleen, left hemidiaphragm, stomach, small intestine, colon, abdominal aorta and inferior vena cava; metastases to the abdominal nodes, left lobe of the liver and right adrenal gland; ascites; edema of the legs and scrotum; prominent, superficial

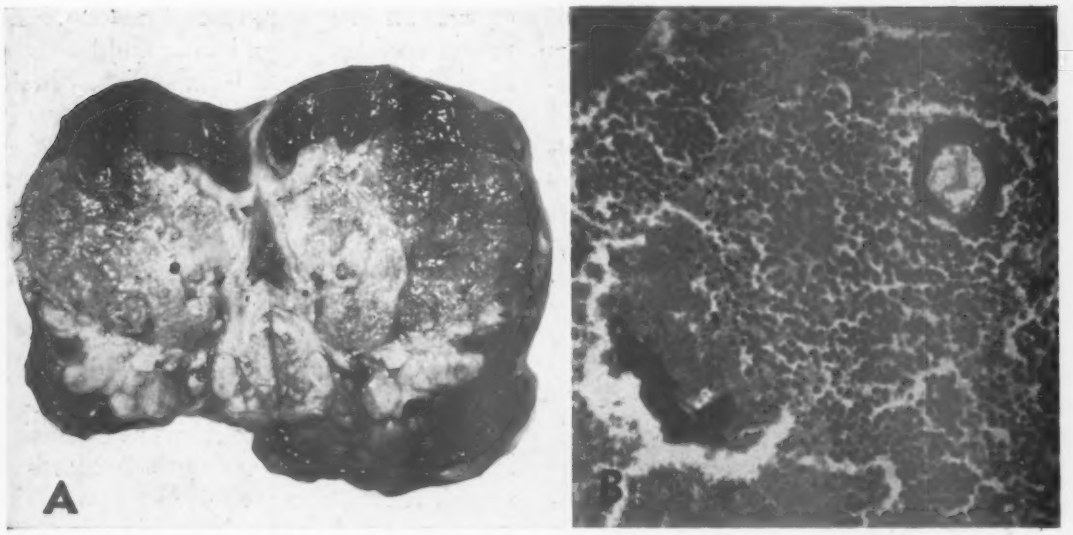

Fig. 3. (*A*) Gross tumor (postmortem) displacing and growing into spleen superiorly and displacing intestines right inferiorly. (*B*) Neuroblastoma with necrosis showing calcification, and calcification in vessel walls.

abdominal veins; abdominal scars from previous operation; atelectasis of lower lobes of lung; marasmus; anemia; hemorrhagic content in intestine.

Case III. T. D., male, white, aged thirteen months, was admitted to the Buffalo Children's Hospital on November 11, 1946, for unilateral exophthalmos and a mass in the left upper quadrant of the abdomen, of two months' duration. In abdominal films, innumerable small calcifications were seen in a large mass in the left upper quadrant. Biopsy of the mass at laparotomy proved it to be microscopically a malignant neurogenic tumor of the neuroblastoma group with extensive calcification. Under nitrogen mustard therapy, there was remarkable temporary remission in exophthalmos and bony metastases on two occasions.

DISCUSSION

Our experience of seeing in eighteen months, 3 successive cases of retroperitoneal neuroblastoma with calcification demonstrated on the roentgenograms is an unusual one. From our review of the literature, for the past forty-five years, we found only 18 cases of neuroblastoma in which calcification was noted roentgenologically. The majority of tumors had their origin in the retroperitoneal tissues. Wyatt and Farber[15] reported 6 cases; Shaffer[13] 3; Parsons and Platt[11] 2; the other 7[1,3,4,6,9,10,14] were described as isolated cases.

Comment has been made in the literature on the mechanism of calcification in neuroblastoma. The consensus is that the calcification represents the dystrophic type

Fig. 4. Roentgenogram of abdomen (anterior view) with calcification in left upper field.

occurring spontaneously on the basis of regressive changes. Such is the mechanism in our 3 cases where degeneration and necrosis were observed microscopically and where calcification was noted by the roentgenologist and pathologist before therapy with roentgen radiation and nitrogen mustard was instituted. In Case II calcification also involved vessel walls in several areas. Whether necrosis produced by treatment led to additional calcification must be considered; post-therapeutic films in our cases showed no appreciable changes in density. Our first case with its blood calcium reading of 12.4 mg. per 100 cc. after the appearance of generalized bony metastases raises the possibility of metastatic calcification, but no postmortem evidence was on hand to substantiate such a mechanism.

The question may be asked how far calcification seen on the roentgenogram in a retroperitoneal mass bears significance in differential diagnosis. The two lesions most frequently causing retroperitoneal masses in childhood are neuroblastoma and Wilms' tumor. In our cases, calcification was interpreted to suggest a diagnosis of neuroblastoma (Case I) and to veer from a diagnosis of Wilms' tumor (Case II). Comparative analysis of the literature on roentgenologic calcification in neuroblastoma and Wilms' tumor offers us the following information: In over one hundred articles, we found 18 cases of neuroblastoma with roentgenologically detected calcification. In a review of seventy-five articles on Wilms' tumor, we collected only 3 cases[1,8] with calcification demonstrated on the roentgenogram. The occurrence of calcification in retroperitoneal masses such as benign tumors, tuberculous lymphadenitis, hematomas, and old abscesses must be kept in, mind.

One may consider whether any prognostic significance can be placed on calcification in neuroblastoma. On this point, no statistics are available. Two diametrically opposed views however exist. According to the first, necrosis with calcification is an expression of spontaneous "healing." Proponents of the second view hold that necrosis in an untreated tumor is an indication of rapid growth. In our Cases I and II, death occurred within two years of admission to the hospital despite therapy. Case III showed only temporary remission of exophthalmos and bony metastases under nitrogen mustard treatment.

As regards therapy, our cases bring out several points. In not one of our patients at laparotomy was surgical removal feasible because of local invasion and metastases. Case I illustrates the extreme radiosensitivity with which some neuroblastomas respond. After therapy, the large abdominal mass regressed so that it could no longer be felt on abdominal palpation; at laparotomy only small nodules were identified. Rypins[12] and Farber[5] attest to the radiosensitivity of neuroblastoma. On the other hand, Askin and Geschickter[2] state, "Neuroblastoma fails to respond to deep x-ray therapy." Our Case II might be taken to support this statement.

Our Case I is of singular pathologic interest in relation to the presence of tuberculoid lesions in metastatic neuroblastoma of a cervical lymph node. No such lesions in metastatic neuroblastoma have been previously recorded. Hartz and van der Sar[7] reported the first and thus far only case of neuroblastoma (neurocytoma) with pseudotubercles in the primary tumor; they called attention to the similarity between these pseudotubercles and those of dysgerminoma. Pseudotubercles are apparently a reaction to regressive changes. Of further pathologic interest in our first case is the postmortem finding of ganglioneuroma at the site of the original tumor from which two biopsies had shown neuroblastoma. The combination of ganglioneuroma and neuroblastoma has been noted in the literature by various authors.

SUMMARY

Three successive cases of retroperitoneal neuroblastoma seen in eighteen months are reported for the following reasons:

In all three, calcification was detected in the roentgenograms during the life of the patient. Two cases received nitrogen mustard therapy. Tuberculoid lesions were observed histopathologically in metastases to cervical lymph nodes of one case.

We are indebted to Dr. Samuel Sanes for advice and criticism.

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ROENTGEN THERAPY ALONE IN THE TREATMENT OF ADVANCED CERVICO-UTERINE CANCER, INCLUDING EXTENSIVE POST-OPERATIVE RECURRENCES*

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Curie Foundation
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FIFTY-SIX uncured cases of Stage I cancer of the cervix and uterus were followed until death of the patients. In Figure 1, these cases have been divided into four groups according to site of persistent disease.

A—12 local recurrences
B—14 medial parametrial recurrences
C—10 lateral parametrial recurrences (lymph nodes developed on the wall)
D—20 distant metastases (iliac, abdominal or supraclavicular lymph nodes, visceral metastasis, lung, liver, bones)

Figure 1 shows that more than a third of these Stage I cases were beyond the stage of curability by radiotherapy because distant metastases had already occurred. In groups A, B, and C, however, cure might perhaps be possible from improved technique.

In order to explore this possibility and

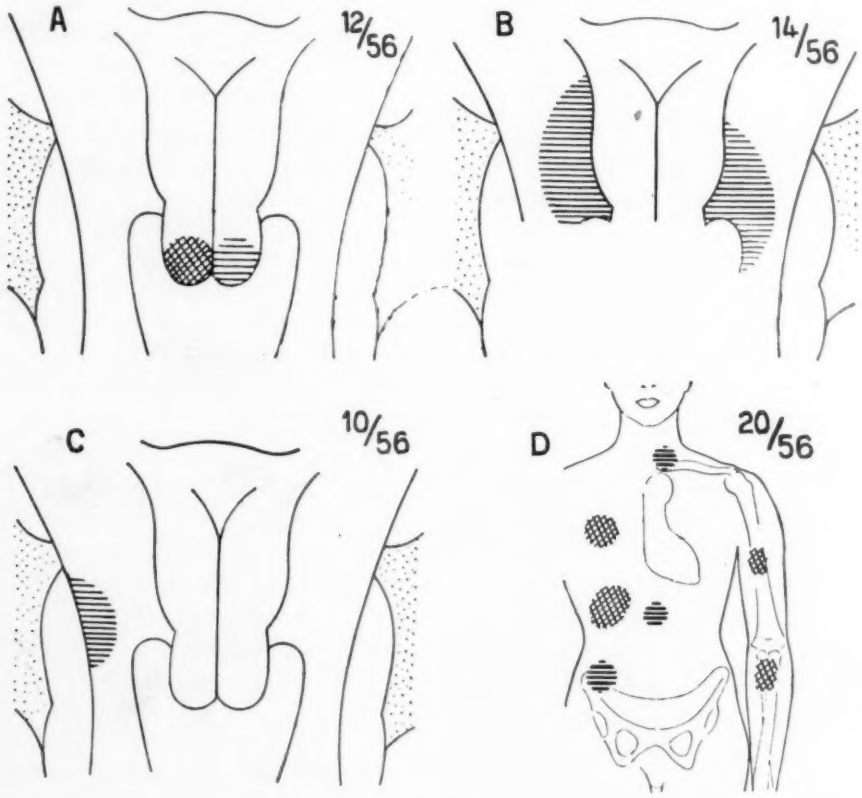

FIG. 1

* From the Curie Foundation, Paris. Presented at the Thirtieth Annual Meeting, American Radium Society, Chicago, Ill., June 20–22, 1948.

to obtain more accurate information concerning the effective dosage and technique, 78 cases of advanced uterine cancer were treated by roentgen irradiation alone from 1930 to 1942.

Of 72 cases (Stages III and IV) irradiated with 200 kv., 14 are alive and apparently well five years or more after treatment (17 at the maximum).

Of 6 cases treated with 500 kv. there are no survivals. These figures are inconclusive because the number of cases is too small and the technical conditions have not been identical.

HISTOPATHOLOGY AND METASTASES

Among the 78 cases there were:

7 adenocarcinomas of the corpus uteri of which two remain apparently healed after 5 and 14 years.

5 distant metastases which developed rapidly (3 bone, 1 lung, and 1 in the pyloric region).

1 developed a second cancer in the maxillary region.

Grouped according to the stages of disease, there were:

11 in State III.

1 in Stage IV.

2 were postoperative recurrences, 1 of which had a vesicovaginal fistula.

Of the 78 patients treated, 7 were found to have marked involvement of the vagina extending to the vulva, making it impossible to determine the exact origin of the cancer, whether vagina or cervix. Of these 7 patients with extensive vaginal lesions, 4 remain apparently cured after five years.

It seems important to emphasize the better curability of these advanced vaginal cases in contrast to the poorer curability of cases with parametrial involvement extending to the lateral pelvic wall.

In compiling the record of the cured cases, careful attention has been given to the strict clinical classification of the parametrial involvement and we are under the impression that a few cases remained cured despite true involvement of the parametrium. However, none of these cases had edema or pain in the lower extremities, and no case with palpable external iliac lymph nodes reached the five year survival period. One case with obvious lateral parametrial involvement was clinically cured locally, but the patient died of pulmonary metastases.

The cases reported here may be too few for conclusive statistics, but they do indicate some important technical points. The five year survivals have been obtained with roentgen irradiation, using 200 kv., 1 mm. Cu filter, 60 to 70 cm. target skin distance, and 20 r per minute on patients treated from 1930 to 1942.

Fields: In the early cases, the fields were large (20 by 20 cm., 15 by 15 cm.) and they

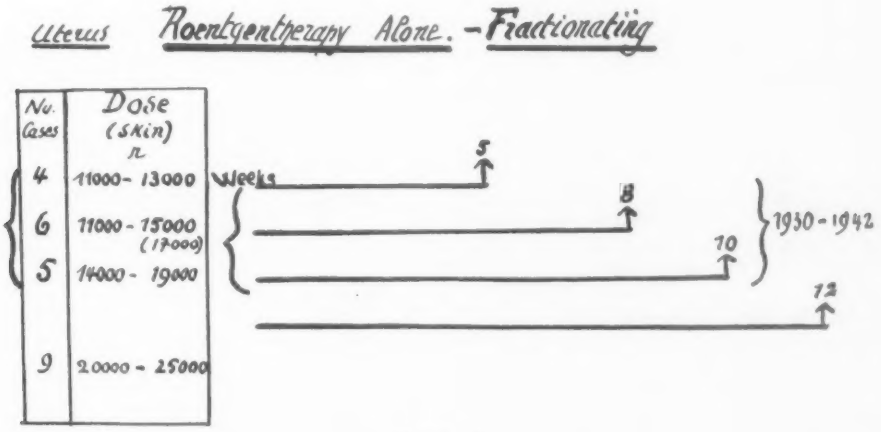

Chart I

overlapped. There were skin, bladder and intestinal sequelae. These large fields have been discarded. At present treatment is started with fields of 150 cm. to 120 cm.; these are decreased to 100 cm., or 80 cm. Sometimes even smaller portals are used toward the end of treatment.

Dosage and fractionation have varied throughout the years. An increased dosage necessitates an increased fractionation to avoid cutaneous, intestinal or vesical complications.

In Chart 1, the first three lines include the 14 cured patients. Patients on the first line received a total skin dose of 11,000 to 13,000 r through six fields, two anterior and four posterior. On the second line the skin dose varies from 11,000 to 17,000 r. Dosage on the third line varies from 14,000 to 19,000 r.

Fractionation for these groups has been increased successively from four or five weeks to eight and to 10 weeks. When the treatment period was under five weeks, the patients presented severe reactions and one of these, treated within twenty-five days, suffered serious skin changes, with late necrosis. This short period has been discarded since 1930. Fractionating the dosage over a period of eight weeks was an improvement and a ten week period was even more satisfactory. It is absolutely necessary for the high doses utilized here.

The patients indicated on the fourth line are not included in the discussion because they are too recent (1943 to 1946).

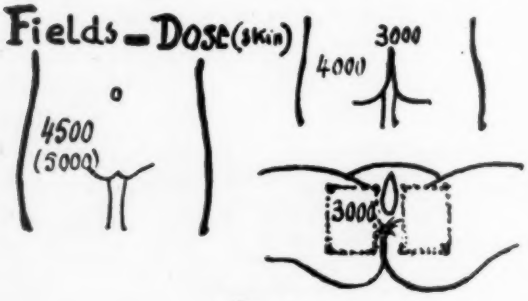

FIG. 2

The doses were fractionated over a period of twelve weeks and this technique is currently employed for advanced cases at the Curie Foundation. The total skin dose varies from 20,000 r to 25,000 r and these very high doses can be attained only by extended fractionation.

Moist skin reactions as well as bladder and intestinal reactions should be avoided whenever possible. It must be planned from the beginning to adhere rigidly to the low daily dosage rates. The dose to any field must not be such that an undue skin reaction is produced. The critical times for the appearance of skin reactions are at the fourth, sixth, eighth, and tenth week intervals. If this reaction is produced too soon, treatment must be suspended and such interruptions should, if possible, be avoided.

The tumor dose for the cured cases has been 4,300 r to 7,100 r.

Figure 2 shows roughly the doses per field. The anterior pelvic (iliac) field received 4,000 r to 4,500 r with a maximum of 5,000 r. The posterior pelvic (oblique sciatic) field received 4,000 r with a maximum of 4,500 r. The middle sacral field received 2,500 r to 3,000 r maximum dose. To these fields were added two small perineal fields (5 by 6 cm.) directed toward the obturator foramen. They constitute excellent ports of entry for the parametria.

Since 1943–1945 we have been irradiating, when possible, through a direct intravaginal field which receives a dose varying from 2,500 to 3,000 r or more.

Thus, it may be possible in radiosensitive cases to deliver an adequate dose (5,000 r or more) to sterilize the parametria. We have rarely used the transverse field, and none of the patients reported here as cured has been irradiated through this field.

Curie Foundation
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Vol. 63, No. 2

DEPARTMENT OF TECHNIQUE

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PHOTOELECTRIC TIMING IN DIAGNOSTIC ROENTGENOLOGY*

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THE production of roentgenograms of the highest quality requires three essentials:

1. Sharpness of detail.
2. Contrast.
3. Uniformity of density.

The roentgenologist can control detail and contrast by the use of standard techniques and appropriate equipment. On the other hand, uniformity of density, while equally essential, has not lent itself to such ready control. Heretofore, uniform and desirable density has been dependent on the technician's ability to accurately gauge the exposure time after an estimation of the patient's thickness and probable density. In so doing, the technician, whether aware of it or not, attempts to judge and regulate the total effective radiation reaching the film. The ideal method of regulating film density and hence the determination of the exposure time, would be by a radiation meter so calibrated as to parallel film speed.

In roentgenology, radiation meters have long been a problem. After extensive investigation, two solutions have evolved:

1. The use of ionization chambers
2. Pholoelectric tubes in conjunction with fluorescent screens.

In the wavelengths employed in diagnostic roentgenology, it has been shown by Morgan that the use of the ionization chamber has certain objectionable features, and in addition its response does not parallel film speed. Early photoelectric timers developed in Europe used low gain photoelectric cells and vacuum tube amplifiers, the operation being in critical and unstable conditions. They were laboratory type instruments and not satisfactory for regular clinical use. With the development in 1940 of the photomultiplier type photoelectric tube, these difficulties were largely eliminated. In 1941 Morgan and Hodges announced the first practical timer and used this tube. In 1944 they described its adaptation to all phases of roentgenography. In the interval since, they have published many observations on the general photometric principles involved. Their work merits careful study by anyone interested and no paper on the subject could be complete without drawing heavily on their observations.

To a limited extent, photoelectric timers are now available. They are included in all photoroentgen units with very satisfactory results. In a more limited way, they are

* Delivered before the Canadian Association of Radiology, Kingston, Canada, January, 1948.
† Associated with the Department of Veterans Affairs and the Department of Health and Welfare.

being used in routine chest roentgenography and no doubt its use will soon be rapidly extended.

The observations on which this paper are based extend over a period of three years. In this time one of us (I.N.) has constructed at least six working models and each has had a number of major and minor changes. They have been used in routine roentgenographic practice for approximately 50,000 exposures with several different types of apparatus, and in all types of work including non-screen, screen, Potter-Bucky, and gastric spot film technique.

The main components of a photoelectric timer consist of the 931 phototube connected in series with a condenser, thyratron and relay, supplemented by the appropriate power packs and controls. The 931 tube is a so-called multiplier type; that is, the initial weak current is amplified within the tube itself by secondary electron emission from a series of nine electron mirrors or dynodes. The gain in signal strength is in the nature of 2,000,000, and even from the low initial value provided by a fluorescent screen, the output is several microamperes. Besides being extremely sensitive, the tube is stable, its response to light is linear, and its maximum sensitivity approaches that of commercial roentgen films in the region of the spectrum in which most fluorescent screens respond. The tube is placed in a lightproof receptacle along with a fluorescent screen below the object to be roentgenographed and below the film or cassette. When the exposure is initiated, the fluorescent material adjacent to the tube lights up in proportion to the radiation received and which is also identical to that received by the overlying film, provided no radiopaque holder or cassette is used. The tube then passes a current in direct linear relation to the quantity of light received. This current is passed to the condenser and when the potential of the condenser reaches a predetermined level, the thyratron ionizes and allows a current to trip the relay and terminate the exposure.

From this brief description it might be expected that the phototimer would be a total radiation detector. In practice it falls somewhat short of this ideal as will be demonstrated below. This arises primarily through the failure of any type of fluorescent material now available to entirely parallel the response of films under all conditions; and secondarily through the filtration effect of screens and cassettes. Utilizing the latter, the phototimer is not independent of the quality of kilovoltage used. The inherent discrepancy may be enormously distorted by slight errors in design and construction. To these problems might also be added an additional one which also plays a considerable part in the uniformity of the end result; that is, the area and arrangement of the fluorescent scanning screen in relation to the tube in the detector unit. We believe considerable work is still necessary before the best possible practical apparatus is produced.

NON-SCREEN TECHNIQUE

The response of the phototube detector with a suitable fluorescent screen and appropriate filter closely parallels the sensitivity of non-screen films under all circumstances within the range of radiation quality used in medical roentgenology. The timer under these circumstances is an adequate quantitative radiation detector and will yield consistently uniform roentgenograms for the area exposed, irrespective of the factors used. It is independent of distance, milliamperage, kilovoltage, thickness or density of the subject within wide limits. For example, roentgenograms may be taken of a part utilizing widely different penetration, such as the wrist at 55–65–75 kv., with no appreciable change in density, other factors in this particular case being constant. Likewise thin and thick parts may be taken with no factor changed and the phototimer at the same sensitivity, such as a finger and knee, and of course similar results for other parts of intermediate thickness. It is apparent from this that technically good films are entirely dependent on accurate placing of the desired

anatomical part by the technician in relation to the scanning aperture of the tube.

SCREEN TECHNIQUE

Attention has already been directed to Morgan's finding that the phototimer and the speed of films taken in a cassette did not run parallel. He proposed an automatic interlocking control of the main potential selector of the roentgen-ray machine and the phototimer, so that raising the voltage correspondingly adjusts the sensitivity of the phototimer, thus compensating for the effect of voltage change on the amount of radiation absorbed by the rear screen, the back of the cassette, and the cover of the detector. Our experience has been in agreement with the disrupting effect of screen-cassette filtration, but we believe further work may discover other ways to eliminate this trouble. In chest roentgenography with our current phototimer model, a change of 10 kv. from 60 to 70 kv. has little effect on film density in either a thin or moderately heavy subject. The timer compensates for this, as well as being relatively independent of subject thickness, i.e., two films are shown on each of two subjects of 18 and 25 cm. respectively, taken at 60 and 70 kv. and all are of approximately equal density.

As already intimated, we do not accept our present standard of results as either entirely satisfactory or the best possible. We should expect, however, that chest roentgenography is one place where photoelectric timers will be an advantage.

EXPOSURES UTILIZING A GRID

The same difficulties are encountered here as in techniques employing a cassette without a grid, and in addition added controls are necessary to change timer sensitivity to correspond to the longer exposure and the type of screen used. We have had less experience with this type of work in routine cases, as our cassettes are poorly matched and have too great a filtration effect. We have found it necessary to select an approximately correct kilovoltage setting, and if this is done, uniformly dense roentgenograms result. Roentgenograms of such diverse parts as skull, all parts of the spine, shoulder, sternum, kidney and bladder area, gallbladder, and obstetrical cases are equally satisfactory.

GASTRIC ROENTGENOGRAPHY

It is in this field that I believe the phototimer fully justifies itself and in which we have used it routinely for the past thirty months. No claim is made that the film density is entirely uniform, but we believe the uniformity is greater than we could accomplish by manual setting, and with much less trouble. For only thin patients on the one hand, and heavy at the other extreme, say under 100 and over 170 pounds, do we find it advisable to alter the sensitivity of the phototube. The control is not critical and is placed conveniently on the fluoroscopic screen carriage. Diagnostic roentgenograms are obtained from the esophagus to the colon with no change in setting in the great majority of cases. Likewise there is good compensation for kilovoltage change with satisfactory results over a spread of 70 to 95 kv. In selecting apparatus for spot film roentgenography, it is desirable that the arrangement of the phototube be such that the image may be seen during roentgenography as well as during roentgenoscopy. It is also desirable that various sizes of exposure be obtainable. We prefer on an 8 by 10 inch film a choice of a single exposure, two 4 by 10 or four 4 by 5 inch exposures.

CONCLUSION

In selecting any prospective apparatus it should be appraised carefully from the structural, financial and functional aspects.

The equipment should meet certain standards of design. The controls should be simple. It should be backed by good service.

To the expense of the original equipment should be added that of new matched screens and cassettes.

Our experience as to final function is as follows:

(1) In non-screen techniques, extremely uniform results are to be expected, provided the technician uses more rather than less care in the placement of the part. The technical factors are far from critical.

(2) In screen and Potter-Bucky techniques, much better than average uniformity is to be expected. Moderate judgment of factors is demanded of the technician and the same care is usually employed in placement.

(3) In gastric spot film technique, the procedure is simplified, time is saved, and more uniform results obtained.

Medical Arts Building
Ottawa, Ontario

Vol. 63, No. 2

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

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Publisher: Charles C Thomas, 301–327 East Lawrence Avenue, Springfield, Illinois.

Issued monthly. Annual subscription: United States, Mexico, Cuba, Central and South America, $10.00; Canada, $11.00; other countries, $12.00. Advertising rates submitted on application. Editorial office, 110 Professional Building, Detroit 1, Michigan. Office of publication, 301–327 East Lawrence Avenue, Springfield, Illinois. Information of interest to authors and readers will be found on page iv.

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EDITORIAL

STUDIES ON FIBROSIS OF THE PANCREAS

QUITE recently Lowe, May, Stauffer and Neuhauser[1] carried out a series of studies on patients with fibrosis of the pancreas, first to determine, if possible, an acceptable physiologic explanation for the ravenous appetite of patients with fibrosis of the pancreas and its abatement with the administration of dried pancreas, and second, to determine whether or not the pancreas is involved in the production of an enterogastrone-like substance which might play a role in the "duodenal mechanism" which Gershon-Cohen[2] described as regulating the motor and sensory activity of the stomach.

It has long been observed and recorded that orally ingested fat remains longer in the stomach than other foods and furthermore that gastric motility and gastric secretion are decreased following its administration, and it has been further observed that fat placed directly in the duodenum causes a decrease in both peristalsis and the secretory activity of the stomach.

Many investigators have carried out studies which indicated that neuronal influences are implicated in the inhibition of gastric secretion and motility, and Farrell and Ivy[3] demonstrated that humoral agents are also involved, since when fat was fed, transplanted and denervated gastric mucosa was observed to act in a way indistinguishable from that portion which had remained in situ. This observation of Farrell and Ivy's was subsequently confirmed by others, namely Lim, Loo and Liu.[4]

An attempt to isolate the humoral material responsible for these effects was successful in 1930 when Kosaka and Lim[5] demonstrated that a saline or hydrochloric acid extract of duodenal mucosa which had previously been in contact with fat was able to inhibit gastric activity when administered intravenously, and furthermore, that no such effect could be demonstrated when an extract of mucosa which had not been exposed to fat was administered. They proposed that the agent responsible for gastric inhibition be called enterogastrone, and subsequently this has been isolated in pure form.

Ivy and his coworkers[6] recently demonstrated that relatively pure enterogastrone was not capable of exerting its effect on the denervated dog's stomach but that fat was still able to inhibit hunger contractions in these denervated stomachs.

While enterogastrone has been isolated in increasingly pure form little is known of its chemical structure. It has been determined, however, that none of the digestive products normally resulting from hydrolysis of fat can produce an enterogastrone-like effect and, furthermore, exposure of gastric mucosa to fat will not yield enterogastrone.

Nothmann and Wendt[7] demonstrated in 1932 that the phenomenon of gastric in-

[1] Lowe, C. U., May, C. D., Stauffer, H. M., and Neuhauser, E. B. D. Fibrosis of pancreas; enterogastrone and "duodenal mechanism" in relation to increased appetite. *Am. J. Dis. Child.*, Jan., 1950, *79*, 91–98.

[2] Gershon-Cohen, J. Duodenal mechanism regulating motor and secretory activity of stomach; its roentgenographic disturbance in duodenal ulcer. *Radiology*, 1947, *48*, 232–238.

[3] Farrell, J. I., and Ivy, A. C. Studies on motility of transplanted gastric pouch. *Am. J. Physiol.*, 1926, *76*, 227.

[4] Lim, R. K. S., Loo, C. T., and Liu, A. C. Observations on secretion of transplanted stomach. *Chinese J. Physiol.*, 1927, *1*, 51–62.

[5] Kosaka, T., and Lim, R. K. S. Demonstration of humoral agent in fat inhibition of gastric secretion. *Proc. Soc. Exper. Biol. & Med.*, 1930, *27*, 890.

[6] Harris, S. C., Grossman, M. I., and Ivy, A. C. Role of vagus nerves in inhibition of gastric motility by fat and by intestinal and urinary extracts. *Am. J. Physiol.*, 1947, *148*, 338–343.

[7] Nothmann, M., and Wendt, H. Über eine regulatorische Funktion des Pankreas für die Magenentleerung nach Fettmahlzeit. *Arch. f. exper. Path. u. Pharmakol.*, 1932, *168*, 49–56.

hibition by fat was no longer present in pancreatectomized dogs and it had been observed that fat seems to leave the stomach even more rapidly than simple barium sulfate in the pancreatectomized dogs. Gershon-Cohen[8] and his associates, in roentgenological studies on human beings, demonstrated what they termed the "duodenal mechanism," namely that when fat fed to normal patients reached the duodenum, the pylorus closed and remained closed for long periods. When fat was placed directly in the duodenum, the mechanism operated immediately, and the farther down the duodenum fat was placed, the less well the reflex could be demonstrated.

It has been observed that loss of pancreatic exocrine function results in increased appetite and that the oral administration of dried pancreas causes an abatement of the increased appetite. These findings suggest that the pancreas is involved in the "duodenal mechanism" and that, possibly, enterogastrone is the hormone responsible for the presence of this mechanism.

It was in an attempt to elucidate these problems that the studies of Lowe[1] and his associates were instituted and from their observations there seemed to be no apparent relationship between the pyloric opening time of the stomach and the presence or absence of fat in the barium sulfate in either the normal subjects or those with fibrosis of the pancreas. It was possible from their experiments to confirm in patients with fibrosis of the pancreas the observations that Nothmann and Wendt and others had made on pancreatectomized dogs and they showed that the normal relationship between gastric motility and emptying time and a fatty meal is not present in patients with fibrosis of the pancreas. On the contrary, their experiments led them to believe that there is decreased gastric emptying time following a fatty meal. The administration of pancreatin U.S.P. thirty minutes before a fatty meal produces an emptying progression in patients with fibrosis of the pancreas quite similar to that found in normal patients following a fatty meal.

Furthermore, the bowel pattern in children with fibrosis of the pancreas was not unusual either with or without administration of fat, but in normal children the bowel pattern, when fat was added, was typical of the clumping pattern seen in deficiency diseases. This identical type of pattern was also seen in two children with fibrosis of the pancreas after the administration of pancreatin.

From their experimental observations, Lowe and associates concluded that the humoral agent responsible for the "duodenal mechanism" depends on either a normal pancreas in situ or the products of a normal pancreatic digestion, and they concluded that on the basis of the present evidence, one cannot differentiate between these two possibilities. The pancreatin given by mouth might have been the actual source of this hormone or might have aided in its elaboration when fat was present in the duodenum.

They were unable to interpret clearly the significance of the deficiency type of bowel pattern observed in normal subjects and in patients with fibrosis of the pancreas. The obvious explanation for it would be that it (the deficiency pattern) appears whenever excess fat is present in the bowel. But, they conclude, as "attractive as that explanation might seem, it does not explain the failure of this pattern to appear in untreated patients with fibrosis of the pancreas or its appearance in them when they were fed pancreatin. A more logical explanation, particularly in view of the work of May and McCreary, who could frequently erase the 'clumping pattern' in patients by the administration of methacholine chloride, is that this intestinal picture is due to the hormone which is re-

[8] Gershon-Cohen, J., and Shay, H. Experimental studies on gastric physiology in man; study of pyloric control. Rôle of milk and cream in the normal and in subjects with quiescent duodenal ulcer. Am. J. Roentgenol. & Rad. Therapy, 1937, *38*, 427–446. Shay, H., Gershon-Cohen, J., and Fels, S. S. Rôle of upper small intestine in control of gastric secretion. *Ann. Int. Med.*, 1939, *13*, 294–307.

sponsible for the 'duodenal mechanism.' The patient with steatorrhea no doubt has residual fat in his intestine at all times, and therefore when barium sulfate is administered one observes the intestinal pattern which normally is present only following the feeding of fat. However, the response per se is due not to the presence of fat but rather to the hormonal effect it has engendered."

The studies and observations of Lowe, May, Stauffer and Neuhauser confirmed a long well known fact that in normal subjects orally administered fat results in delayed gastric emptying[9] and in patients with fibrosis of the pancreas the feeding of fat does not have this effect. Moreover, when pancreatin is fed to patients with fibrosis of the pancreas thirty minutes before a meal with fat, delayed gastric emptying occurs.

The careful observations which this group have carried out on the normal and on patients with fibrosis of the pancreas should stimulate further studies in this direction in the hope that the exact mechanism responsible for the control of the pylorus might be found.

[9] Macy, I. G., Reynolds, L., Souders, Helen J., and Olson, Mary B. Normal variation in gastrointestinal response of healthy children. AM. J. ROENTGENOL. & RAD. THERAPY, 1940, *43*, 394–403.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa. Annual meeting: Jefferson Hotel, St. Louis, Mo., Sept. 26–29, 1950.

American Radium Society
Secretary, Dr. H. F. Hare, 605 Commonwealth Ave., Boston, Mass. Annual meeting: Roosevelt Hotel, New York, N. Y., May 25–26, 1950.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N.Y. Annual meeting: 1950, to be announced.

American College of Radiology
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6. Annual meeting: 1950, to be announced.

Section on Radiology, American Medical Association
Secretary, Dr. Paul C. Hodges, 950 E. 59th St., Chicago, Ill. Annual Meeting: San Francisco, Calif., June 26–30, 1950.

Alabama Radiological Society
Secretary, Dr. W. W. Anderson, Tuscaloosa, Ala. Meets time and place Alabama State Medical Association.

Arizona Association of Pathologists and Radiologists
Secretary, Dr. R. Lee Foster, 507 Professional Bldg., Phoenix, Ariz. Two regular meetings a year. The annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Atlanta Radiological Society
Secretary, D. W. W. Bryan, 490 Peachtree St., N.E., Atlanta, Ga. Meets monthly, except during three summer months, on second Friday evening.

Brooklyn Roentgen Ray Society
Secretary, Dr. J. J. Daversa, 345 75th St., Brooklyn, N. Y. Meets monthly fourth Tuesday, Oct. through April.

Buffalo Radiological Society
Secretary, Dr. Mario C. Gian, 610 Niagara St., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse N. Y. Meets January, May, November.

Central Ohio Radiological Society
Secretary, Dr. Paul D. Meyer, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, December, February, April, and June at Seneca Hotel, Columbus, Ohio.

Chicago Roentgen Society
Secretary, Dr. John H. Gilmore, 720 N. Michigan Ave., Chicago 11, Ill. Meets second Thursday of each month October to April inclusive at the University Club.

Cincinnati Radiological Society
Secretary, Dr. E. C. Elsey, 927 Carew Tower, Cincinnati 2, Ohio. Meets last Monday of each month, September to May, inclusive.

Cleveland Radiological Society
Secretary, Dr. J. R. Hannan, Cleveland Clinic, Cleveland 6, Ohio. Meetings at 6:30 P.M. on fourth Monday of each month from October to April.

Colorado Radiological Society
Secretary, Dr. Paul E. RePass, 306 Republic Bldg., Denver 2, Colo. Meets third Friday of each month at University of Colorado Medical Center or at Denver Athletic Club.

Connecticut Valley Radiologic Society
Secretary, Dr. E. W. Godfrey, 1676 Boulevard, West Hartford, Conn. Meets second Friday Oct. and April.

Dallas-Fort Worth Roentgen Study Club
Secretary, Dr. X. R. Hyde, Medical Arts Bldg., Fort Worth, Texas. Meets in Dallas on odd months and in Fort Worth on even months, on third Monday, 7:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. W. G. Belanger, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434-30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Florida Radiological Society
Secretary, Dr. F. K. Hurt, Riverside Hospital, Jacksonville, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

Georgia Radiological Society
Secretary, Dr. Robert Drane, DeRenne Apartments, Savannah, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

Greater Miami Radiological Society
Secretary, Dr. David Kirsh, 712 duPont Bldg., Miami 32, Florida. Meets last Wednesday of each month at 8:00 P.M. at Veterans Administration Regional Office.

Houston X-ray Club
Secretary, Dr. Curtis H. Burge, 3020 San Jacinto St. Houston 4, Texas. Meets fourth Monday each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Illinois Radiological Society
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. William M. Loehr, 712 Hume-Mansur Bldg., Indianapolis 4. Meets second Sunday in May.

Iowa X-Ray Club
Secretary, Dr. Arthur W. Erskine, 326 Higley Bldg., Cedar Rapids, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. Special meetings by announcement.

Kansas Radiological Society
Secretary, Dr. Anthony F. Rossitto, Wichita Hospital, Wichita, Kan. Meets annually with State Medical Society.

Kentucky Radiological Society
Secretary, Dr. W. C. Martin, 321 W. Broadway, Louisville. Meets annually in Louisville on first Saturday in Apr.

Kings County Radiological Society
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Wybren Hiemstra, 1414 S. Hope St., Los Angeles 15, Calif. Meets second Wednesday each month at Los Angeles County Medical Assn. Building.

Louisiana Radiological Society
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

* Secretaries of societies are requested to send timely information promptly to the Editor.

LOUISVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS
Secretary, Dr. R. D. McDuff, 220 Genesee Bank Bldg., Flint 3, Mich.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. T. J. Pfeffer, 839 N. Marshall St., Milwaukee 2, Wis. Meets monthly on second Monday at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Chauncey N. Borman, 802 Medical Arts Bldg., Minneapolis 2, Minn. Two meetings yearly, one at time of Minn. State Med. Assn., the other in the fall.

NEBRASKA RADIOLOGICAL SOCIETY
Secretary, Dr. Ralph C. Moore, Nebraska Methodist Hospital, Omaha 3, Nebr. Meets third Wednesday of each month, at 6 P.M. at either Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. George Levene, Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday, Harvard Club.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. F. H. Ghiselin, 111 East 76th St., New York 21, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

NORTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. J. E. Hemphill, 1420 E. Fifth St., Charlotte 4, N. C. Meets in May and October.

NORTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings by announcement. Annual session with State Medical Society in May, 1950, at Grand Forks, N.D.

NORTHERN CALIFORNIA RADIOLOGICAL CLUB
Secretary, Dr. R. L. Ayers, 726 4th St., Marysville, Calif. Meets at dinner last Monday, every second month, except June, July and August.

OHIO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. E. C. Elsey, 927 Carew Tower, Cincinnati 2, Ohio.

OKLAHOMA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. W. E. Brown, Tulsa, Okla. Three regular meetings annually.

OREGON RADIOLOGICAL SOCIETY
Secretary, Dr. Selma Hyman, Univ. of Oregon Medical School, Portland, Oregon. Meets monthly 2nd Wednesday, 8:00 P.M.

ORLEANS PARISH RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY
Secretary, Dr. S. J. Hawley, 1320 Madison St., Seattle 4, Wash. Meets annually in May.

PACIFIC ROENTGEN SOCIETY
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY
Secretary, Dr. J. M. Converse, 416 Pine St., Williamsport. Annual Meeting: Penn Harris Hotel, Harrisburg, Pa., May 12–13, 1950.

PHILADELPHIA ROENTGEN RAY SOCIETY
Secretary, Dr. G. P. Keefer, 1930 Chestnut St. Meets first Thursday each month October to May, at 8:00 P.M., in Thomson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY
Secretary Dr. E. J. Euphrat, 3500 Fifth Ave., Pittsburgh 13, Pa. Meets 6:30 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

QUEENS ROENTGEN RAY SOCIETY
Secretary, Dr. J. E. Goldstein, 88-29 163rd St., Jamaica 3, N. Y. Meets fourth Monday of each month except during the summer.

RADIOLOGICAL SECTION, BALTIMORE MEDICAL SOCIETY
Secretary, Dr. Harry A. Miller, 2452 Eutaw Place, Baltimore. Meets third Tuesday each month, Sept. to May.

RADIOLOGICAL SECTION, CONNECTICUT MEDICAL SOCIETY
Secretary, Dr. Fred Zaff, 135 Whitney Ave., New Haven, Conn. Meets bimonthly on second Wednesday.

RADIOLOGICAL SECTION, DISTRICT OF COLUMBIA MEDICAL SOCIETY
Secretary, Dr. K. C. Corley, 1835 Eye St., N. W., Washington, D. C. Meets Medical Society Auditorium, third Thursday, Jan., March, May, Oct. at 8:00 P.M.

RADIOLOGICAL SECTION, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Roy G. Giles, Temple, Texas.

RADIOLOGICAL SOCIETY OF NEW JERSEY
Secretary, Dr. Benjamin Copleman, 280 Hobart St., Perth Amboy, N. J. Meets annually at Atlantic City at time of State Medical Society and mid-winter at Elizabeth, N. J.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary, Dr. Ralph E. Alexander, 101 Medical Arts Bldg. Meets monthly on third Monday from October to May, inclusive, 8 P.M. at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY
Secretary, Dr. Maurice D. Frazer, 1037 Stuart Bldg., Lincoln, Nebr.

ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. C. J. Nolan, 737 University Club Bldg., St. Louis 3, Mo. Meets fourth Wednesday each month, except June, July, August, and September.

SAN DIEGO ROENTGEN SOCIETY
Secretary, Dr. R. F. Niehaus, 1831 Fourth Ave., San Diego, Calif. Meets monthly, first Wednesday at dinner.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION
Secretary, Dr. D. R. MacColl, 2007 Wilshire Blvd., Los Angeles 5, Calif.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. Harold L. Shinall, St. Joseph's Hospital, Bloomington, Ill.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

SOUTH CAROLINA X-RAY SOCIETY
Secretary, Dr. T. A. Pitts, Baptist Hospital, Columbia, S. C. Meets in Charleston first Thursday in November, also with South Carolina State Medical Association.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. J. M. Frère, 707 Walnut St., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas. Next meeting, Dallas, Texas, February 3 and 4, 1950.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May inclusive. Room 203, Service Memorial Institute, 426 N. Charter St., Madison.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. J. H. Walker, 1115 Terry Ave., Seattle 1, Wash. Meets fourth Monday each month, October through May, College Club, Seattle.

Wisconsin Radiological Society
Secretary, Dr. Irving I. Cowan, 425 E. Wisconsin Ave., Milwaukee 2, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-Ray Study Club of San Francisco
Secretary, Dr. W. F. Reynolds, University of California Hospital, San Francisco. Meets from January to July at Lane Hall, Stanford University Hospital, and from July to December at San Francisco Hospital.

Cuba

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Mexico

Sociedad Mexicana de Radiologia y Fisioterapia
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 p.m.
Medical Members' meeting, on third Friday in each month at 5:00 p.m., 32 Welbeck St., London, W 1.

Faculty of Radiologists
Honorary Secretary, Dr. J. F. Bromley, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 p.m. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary, Dr. E. M. Crawford, 1535 Sherbrooke St., West, Montreal 26, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electrologie et de Radiologie Médicales
Secretary, Dr. Origéne Dufresne, 4120 Ontario St., East, Montreal, P. Q.

Australian and New Zealand Association of Radiologists
Honorary Secretary, Dr. Alan R. Colwell, 135 Macquarie St., Sydney, N.S.W.
Honorary Secretaries, State Branches:
New South Wales, Dr. E. W. Frecker, 135 Macquarie St., Sydney.
Victoria, Dr. T. I. Tyrer, 3 Lockerbie Court, East St. Kilda.
Queensland, Dr. J. Adam, 131 Wickham Terrace, Brisbane.
South Australia, Dr. R. de G. Burnard, 170 North Terrace, Adelaide.
Western Australia, Dr. A. M. Nelson, 179-B St. Georges Terrace, Perth.
New Zealand, Dr. E. G. Lynch, 12 Bolton St., Wellington.

South America

Sociedad Argentina de Radiologia
Secretary, Dr. Guido Gotta, Buenos Aires, Argentina. Meetings are held monthly.

Sociedad Argentina de Radiología, Filial del Litoral
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 7:00 p.m., 663 Italia St., Rosario.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Peruana de Radiologia
Secretary, Dr. Julio Bedoya Paredes, Apartado, 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Sociedad de Radiologica, Cancerologia y Fisica Medica del Uruguay
Secretary, Dr. Arias Bellini.

Continental Europe

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 111 Avenue des Alliés, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Ceskoslovenská společnost pro röntgenologii a radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10.30, X-Ray Dept., Akademia Gdansk.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Meets monthly.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad.
USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock, State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly, first Monday, 8 p.m.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société Suisse de Radiologie)
President, Dr. H. E. Walther, Gloriastr. 14, Zürich, Switzerland.

Societa Italiana di Radiologia Medica
Secretary, Prof. Mario Ponzio, Ospedale Mauriziano. Torino, Italy. Meets biannually.

SIXTH INTERNATIONAL CONGRESS OF RADIOLOGY

This is a reminder of the Sixth International Congress of Radiology to be held in London, England, July 23 to 30, 1950. A copy of the Preliminary Programme, together with the necessary forms for completion, has been sent to all members of radiological societies throughout the world. All those planning to attend are urged to register as Members of the Congress as soon as possible.

There are three classes of members: Full Members (including Junior, for those under thirty), Associates accompanying Full Members, and Scientific and Technical Associates. All are reminded that a higher fee will be charged for registrations received after April 1, 1950.

Members wishing to read papers must notify the Secretary-General not later than February 15, 1950, and an abstract should reach him by April 1. Those who have a scientific exhibit to offer must also send details by February 15, 1950.

Application to join one of the tours of Great Britain and Ireland which are being organized for the week following the Congress must be received by February 15, 1950.

All communications should be sent to the Secretary-General, Sixth International Congress of Radiology, 45 Lincoln's Inn Fields, London W.C. 2.

Additional copies of the Preliminary Programme can be obtained from the same address on request, stating the language in which it is desired.

PENNSYLVANIA RADIOLOGICAL SOCIETY

The Pennsylvania Radiological Society will hold its annual meeting on May 12 and 13, 1950, at the Penn Harris Hotel, Harrisburg, Pennsylvania.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

THE RADIOLOGY OF BONES AND JOINTS. By James F. Brailsford, M.D., Ph.D., F.R.C.P., F.I.C.S., Hunterian Professor, Royal College of Surgeons, England, 1934–5, 1943–4; founder and first President of the British Association of Radiologists (now the Faculty of Radiologists); etc. Fourth edition. Cloth. Price, $15.00. Pp. 765, with 615 illustrations. Baltimore: Williams & Wilkins Company, 1948.

In the fourth edition of Brailsford's Radiology of Bones and Joints, the text has been revised, presenting many additional facts collected, since the third edition was published, from the author's own departments of radiology and from every branch of medical science in the world literature. More than two hundred illustrations have been added. The book is again divided into two parts: The first, of 535 pages, deals with the roentgenographic examination of the skeleton from a regional and anatomical standpoint. The second part, of 185 pages, is a general discussion of the abnormalities of the skeleton and of the pathology of bones and joints. The headings of the chapters of the second part are: Developmental Abnormalities and Dystrophies; Generalized Diseases of the Skeleton; Granuloma of Bones, and Bone Tumors. The paper used in the printing of this edition is uniformly good throughout as compared with the previous edition in 1944 when wartime restrictions forced the publisher to use a poorer grade of paper except for those pages on which roentgenograms were reproduced. The reproductions of the numerous roentgenograms are of excellent quality, although some readers may object to the use of printed positives throughout the book. The style of the text is very readable. It contains many references to the literature interspersed with comments from the author's wide experience. The bibliography has been enlarged in this edition so that it includes 15 pages and affords the student much opportunity for study of original sources.

In his preface the author states that his aversion to biopsy is not of "mushroom growth," and that his long training in the histological interpretation of pathological tissues taught him the painful lessons in regard to the fallibility of such interpretation. He deplores the urge to resort to biopsy and to explore what appears to be any unusual or spectacular roentgenographic lesion. In the chapter on Bone Tumors the limitations of biopsy are fully discussed.

In the chapter on Granuloma of Bone the negative roentgenographic period, or the period which elapses between the onset of symptoms and clinical signs and the appearance of roentgenographic evidence, and the positive roentgenographic symptomless period or the period after the disappearance of clinical signs and symptoms during which the roentgenogram still shows departure from the normal, are discussed in detail. For the experienced roentgenologist this may be a repetition of known facts but for the student and young roentgenologist, emphasis laid on these fundamental factors in differential diagnosis is justifiable.

This revised edition contains much that is useful for the students of roentgenology and for the more advanced roentgenologists. However, exception may be taken to the author's stand on the value and place of biopsy in the diagnosis of bone tumors. The numerous illustrative roentgenograms, the revised text which includes disease conditions recently discussed in the literature and the enlarged bibliography are to be especially commended.

R. S. BROMER, M.D.

MODERN TRENDS IN DIAGNOSTIC RADIOLOGY. Edited by J. W. McLaren, M.A., M.R.C.S., L.R.C.P., D.M.R.E., Director, X-ray (Diagnostic) Department, St Thomas's Hospital, London. Examiner in Radiology, University of London. Cloth. Price, $12.00. Pp. 464, with 381 illustrations. New York: Paul B. Hoeber, Inc., 1948.

This book contains a series of brief monographs on a variety of roentgenologic subjects by many different authors. Few are complete and all attempt to bring the reader up to date in particular fields.

The chapters on "Tumors of the Pharynx

and Larynx" by Baclesse, "Principles of Kymography" by McLaren, "Some Aspects of Ventriculography and Encephalography" by Lysholm, and "Cerebral Angiography" by Engeset and Kristiansen appealed to the reviewer particularly. The chapter on "Fetal Abnormalities" included some very excellent illustrations.

Each chapter has its own bibliography, some of which are fairly complete.

The book is easy to read, the paper of good quality, and the illustrations much better than average.

Philip J. Hodes, M.D.

La Chirurgie Biliaire sous contrôle manométrique et radiologique per-opératoire. By Pierre Mallet-Guy, Professeur à la Faculté de Médecine de Lyon, Chirurgien des Hôpitaux; René Jeanjean, Assistant à la Faculté, Ancien interne des Hôpitaux: and Pierre Marion, Chef de clinique à la Faculté, Ancien interne des Hôpitaux. Paper. Price, 1200 fr. Pp. 138, with 170 illustrations. Paris: Masson et Cie., 1947.

This volume covers seven years of work, in the course of which 550 cases have been operated upon under manometric and roentgenological control performed as a part of the surgery. The authors credit P. L. Mirizzi, of Cordoba, Argentina, with the initiation of this conception of biliary surgery. They have substituted for the simple measurement of biliary pressure a graphic, systematic registration of the biliary pressure curve. First an extensive manometric study was carried through on a large series of cases and then a roentgenographic examination with tenebryl in place of lipiodol. In the course of the evolution of their complex operative technique the authors have devised a special operating table placed over the roentgenologic equipment which makes very easy the taking of roentgenograms during biliary intervention. Refinements of technique which have evolved from their experience include a special centering device, a manometer for registering the biliary pressure, and special forceps and sounds for the biliary tract surgery.

The discussion has been divided into a review of cases of biliary hypertonus; cases of hypotonus; cases of stenosis of the common duct; indications for manometric and roentgenological control during operation for vesicular lithiasis and for common duct stones, and for the management of chronic pancreatitis. The 170 illustrations, roentgenographic and photographic, serve to illuminate the text in a most satisfactory manner.

This is a new conception of the technique of biliary tract surgery and it seems must greatly influence the surgical practice of the future.

James T. Case, M.D.

L'uréthrographie. Par R. Guichard, Radiologiste des Hôpitaux de Bordeaux, and H. Duvergey, Ancien Chef de Clinique Urologique à la Faculté de Bordeaux. Préface du Professeur Darget. Paper. Price, 650 fr. Pp. 190 with 175 illustrations. Paris: Masson et Cie., 1948.

This small volume, the result of six years of work and two thousand urethrographic examinations, is devoted exclusively and completely to the roentgenological examination of the urethra. The reviewer knows of no comparable volume in the American literature devoted to this one subject. It is a splendid book and should be indispensable to the urologist for it is written from both the clinical and roentgenological viewpoint. So practical and useful is this little volume that a listing of the main divisions of the work is certainly in order: Introduction; Historical; Anatomy Review; Physiology Review; Technique of Urethrography in the Male; Accidents and Contraindications; Roentgenograms of the Normal Male Urethra; Retrograde Urethrography during Erection (study of one case of priapism before and after incision of the corpora cavernosa); Spasm of the Membranous Sphincter; Urethral Malformations and Plastic Surgery; Foreign Bodies and Urethral Calculi; Traumatism of the Urethra; Urethroprostatic Tuberculosis; Infection of the Urethra and Adnexal Glands; Cellular Infection of Urethroprostatic origin; Fistulae of Urethral Origin; Post-blennorrhagic Narrowing; Tumors of the Urethra; Prostatic Tumors; Dysectasia of the Vesical Neck (all pathological manifestations having as their common effect altered physiology of micturition and prevention of free opening of vesical neck during micturition); Urethrovesical Reflux (reflux of opaque material into ejaculatory duct system during retrograde urethrography in certain acute infections); Urethrography in the Female; Bibliography (covering 272 references to the literature on this subject).

One of the most interesting chapters from the point of view of beautiful roentgenograms re-

produced is that on Prostatic Tumors. The oblique views in cases of prostatic adenoma show many characteristic filling defects, i.e., disappearance of the image of the verumontanum, a constant lengthening of the urethra below the verumontanum varying with the development and site of the adenoma, enlargement of posterior urethra and saber-blade deformity, etc.

This book cannot be recommended too highly to roentgenologists working in close collaboration with urologists (as in nearly all busy hospital services) and not the least part of its attractiveness is the writing itself—the brevity, logic and conciseness so characteristic of the French.

William M. Loehr, M.D.

Die Indikationen zur Röntgen- und Radiumbestrahlung. Von Dr. Med. Habil. R. Glauner, Dozent für Röntgenologie und Strahlenheilkunde, Stuttgart. Paper. Price, DM 7.20. Pp. 128. Stuttgart: Georg Thieme, 1948.

In the introduction to his monograph the author states that after almost half a century of radiation therapy the time has come when a critical review of its present status seems to be in order. While he addresses his remarks also to radiologists, his main purpose is to provide physicians in general practice and in other specialties with definite indications and contraindications for the use of roentgen rays and radium in the treatment of malignant and nonmalignant disease. Therefore all physical and technical details have been omitted, thus facilitating the perusal of the text by the nonradiologist. Some of the thoughts expressed by the author in the introduction are certainly worth while mentioning. He defends the right and the duty of the radiologist to refuse cases unsuitable for irradiation and points out that the mere availability of the necessary apparatus must not influence such a decision. He also emphasizes the fact which is still overlooked at times both here and abroad that therapeutic radiology should only be practiced by those properly trained and qualified.

The subject matter has been arranged under the following headings: Indications in Malignant Disease; in Localized Inflammations, Tuberculosis and Actinomycosis; and Indications in Other Diseases. The latter include diseases of the blood, skin, glands of internal secretion, bones and joints, gynecological disorders, diseases of the male sex organs, the nervous system, the circulatory system, the lungs, the gastrointestinal tract and the eyes. The use of roentgen rays in gas gangrene and diphtheria carriers is discussed briefly. The "therapeutic test irradiation" in the differential diagnosis of mediastinal tumors is also mentioned. In three tables are shown the five year survivals in the most frequently seen malignancies, their incidence in males and females and recommendations for the therapeutic approach, be it surgery, surgery plus irradiation, or irradiation alone.

The American radiologist will be inclined to agree with a good many of the views expressed by the author, but there are occasions where opinions are apt to differ. While it is not possible to go into detail a few examples will be discussed.

In most clinics carcinoma of the cervix, Stage I, is operated on, others use a combination of roentgen rays and radium. Carcinoma of the fundus is considered a surgical subject and irradiation is given following operation; a few clinics favor preoperative irradiation also. In carcinoma of the lip and tongue the cosmetic results of radiation therapy are considered better than that of surgery; the author strongly favors preoperative irradiation in seminoma of the testicle. He is very pessimistic regarding the prognosis in osteogenic sarcoma and feels that simple resection plus intensive irradiation is as good or better than amputation. In the group of inflammatory diseases the author stresses the value of irradiation of the tonsils, especially in persons with frequent attacks of tonsillitis. Therapy should be administered in the symptom free interval. In some forms of tuberculosis, e.g. cervical glands and female pelvis, good results have been reported; however, the former enthusiasm in Germany for irradiation of pulmonary tuberculosis has disappeared.

Among the contraindications to radiation therapy the author lists acne, sycosis barbae, hyperhidrosis, psoriasis and lupus erythematosus.

This monograph should prove of interest to all who desire to become acquainted with the present status of radiation therapy in Germany. Throughout the text a strictly conservative attitude is maintained and the strongly subjective presentation does not detract from its value. After all, in it is reflected the author's credo as a radiotherapist who has the earnest

desire to do what is best for his patients. A brief bibliography is appended.

Ernst A. Pohle, M.D.

Biological Reactions Caused by Electric Currents and by X-rays: A theoretical study of the phenomena of excitation in the nerve by different electric currents and of the biological reactions caused by x-rays, both based upon a common principle. By J. Th. van der Werff, M.D., D.Sc. Cloth. Price, $5.00. Pp. 203, with 38 illustrations. New York: Elsevier Publishing Co., Inc., 1948.

This book, addressed principally to neurophysiologists and radiobiologists, attempts to describe by means of first order differential equations the response of electrically stimulated nerve and of irradiated biological systems. Approximately five-eighths of the book is devoted to the first topic, one-eighth to general introduction, leaving about seventy pages for the section on biological reactions caused by roentgen and gamma rays.

From a strictly scientific point of view, the latter section will prove disappointing in many respects, since no attempt is made to link radiobiological observations to whatever is known of the biochemistry or the biophysics of the biological system. Moreover, much space is lost in emphasizing a similarity between the two classes of phenomena which is purely mathematical formalism and which, within the limited scope of the book, could have been more properly devoted to a more exhaustive and rigorous comparison between theoretical and experimental results.

In the opinion of the reviewer, however, the book drives home the point that some progress can be made in radiobiological theory by the use of differential equations describing biological systems in dynamic equilibrium, and by introducing in the mathematical treatment proper perturbations to describe the action of ionizing radiations.

L. D. Marinelli

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Modern Trends in Diagnostic Radiology. Edited by J. W. McLaren, M.A., M.R.C.S., L.R.C.P., D.M.R.E., Director, X-ray (Diagnostic) Department, St. Thomas's Hospital, London. Examiner in Radiology, University of London. Cloth. Price $12.00. Pp. 464, with 381 illustrations. New York: Paul B. Hoeber, Inc., 1948.

Morgagni's Syndrome—Hyperostosis Frontalis Interna, Virilismus, Obesitas. By Folke Henschen, M.D., Emeritus Professor of Pathology at the Caroline Institute, Stockholm, Sweden. Cloth. Price, 30/-net. Pp. 172, with numerous illustrations and tables. Edinburgh: Oliver and Boyd, 1949.

Untersuchungen über den Lumbalen und Cervikalen Wirbelbandscheibenvorfall. By Prof. Dr. F. Reischauer, Chefarzt der Chirurgischen Klinik der Städt, Krankenanstalten Essen. Paper. Price, $3.00. Pp. 87, with 25 illustrations. Stuttgart: Georg Thieme, 1949.

The Chest and the Heart. Section I, The Chest, edited by J. Arthur Myers, Ph.D., M.D., Professor of Medicine and Preventive Medicine and Public Health, University of Minnesota Medical and Graduate Schools. Section II, The Heart, edited by C. A. McKinlay, M.D., Clinical Associate Professor of Medicine, University of Minnesota Medical School. Two Volumes. Cloth. Price, $25.50. Pp. 1,846, with 1,003 illustrations. Springfield, Illinois: Charles C Thomas, 1948.

Die Durchleuchtungstechnik der Thoraxorgane. By E. A. Zimmer, Privatdozent an der Universität Basel and Chefarzt des Röntgeninstitutes und des Institutes für Physikalische Therapie im Hôpital Cantonal Fribourg. Second enlarged edition. Cloth. Price, $12.50 Fr. bound. Pp. 119, with 66 illustrations. Basel: Benno Schwabe & Co., 1949.

Differential Diagnosis of Chest Diseases. By Jacob Jesse Singer, M.D., F.A.C.P., F.C.C.P., Medical Director of the Rose Lampert Graff Foundation, Beverly Hills; Consultant in Chest Diseases, Cedars of Lebanon Hospital, Los Angeles, California; etc. Cloth. Price, $7.50. Pp. 334, with 171 illustrations. Philadelphia, Lea & Febiger, 1949.

Photoradiography in Search of Tuberculosis. By David Zacks, M.D., Chief of Clinics, Massachusetts Department of Public

Health. Cloth. Price $5.00. Pp. 297, with 270 illustrations and numerous tables. Baltimore: Williams & Wilkins Company, 1949.

Lung Dust Lesions versus Tuberculosis. By Lewis Gregory Cole, M.D., F.A.C.R. Cloth. Pp. 474, with over 450 illustrations. White Plains: American Medical Films, Inc., 1948.

The Bronchus. By S. Di Rienzo, M.D., Assistant Professor of Radiology and Physiotherapy, Chief of the Radiology Department of the Institute of Cancer, The University of Córdoba, Argentina. Translated by Thomas A. Hughes, M.D. Foreword by Richard H. Overholt, M.D. Cloth. Price, $10.75. Pp. 332, with 466 illustrations. Springfield, Illinois: Charles C Thomas, 1949.

The Radiology of Bones and Joints. By James F. Brailsford, M.D., Ph.D., F.R.C.P., F.I.C.S., Hunterian Professor, Royal College of Surgeons, England, 1934–5, 1943–4; founder and first President of the British Association of Radiologists (now the Faculty of Radiologists); etc. Fourth edition. Cloth. Price. $15.00. Pp. 765, with 615 illustrations. Baltimore: Williams & Wilkins Company, 1948.

Bone and Joint Radiology. By Emerik Markovits, M.D., formerly, Scientific Collaborator of the Central Radiologic Institute of the General Hospital (Holzknecht-Institute), Vienna; Head of the Radiologic Department of Elizabeth Hospital of the City of Budapest; etc. Cloth. Price, $20.00. Pp. 446, with 616 illustrations. New York: Macmillan Company, 1949.

Handbook of Orthopaedic Surgery. By Alfred Rives Shands, Jr., B.A., M.D., Medical Director of the Alfred I. du Pont Institute of the Nemours Foundation, Wilmington, Delaware; Visiting Professor of Orthopaedic Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. In collaboration with Richard Beverly Raney, B.A., M.D., Associate in Orthopaedic Surgery, Duke University School of Medicine, Durham, North Carolina, etc. Third edition. Cloth. Price, $6.00. Pp. 574, with 159 illustrations. St. Louis: C. V. Mosby Company, 1948.

Tuberculosis of the Knee-joint. An exposition with special reference to Course and Treatment. Based on studies of the literature and on an analysis of a material of patients observed through many years. By Johannes Mortens. Paper. Price, kr. 30.-. Pp. 550, with numerous tables. Copenhagen: Einar Munksgaard, 1948.

Neoplasms of Bone and Related Conditions: Their Etiology, Pathogenesis, Diagnosis, and Treatment. By Bradley L. Coley, M.D., Attending Surgeon, Bone Tumor Department, Memorial Hospital for Cancer and Allied Diseases; Assistant Professor of Clinical Surgery, Cornell. Cloth. Price, $17.50. Pp. 765, with 622 illustrations and 53 tables. New York: Paul B. Hoeber, Inc., 1949.

Histopathology of the Skin. By Walter F. Lever, M.D., Instructor in Dermatology, Harvard Medical School; Assistant Dermatologist, Massachusetts General Hospital; Associate in Dermatology, Peter Bent Brigham Hospital; Consulting Dermatologist, Massachusetts Eye and Ear Infirmary. Cloth. Price, $10.00. Pp. 449, with 211 illustrations and 8 subjects in color on 4 plates. Philadelphia: J. B. Lippincott Company, 1949.

Handbook of Diseases of the Skin. By Richard L. Sutton, M.D., Emeritus Professor of Dermatology and Syphilology, University of Kansas Medical School, and Richard L. Sutton, Jr., M.D., Associate Professor of Dermatology and Syphilology, University of Kansas Medical School. Cloth. Price, $12.50. Pp. 749, with 1,057 illustrations. St. Louis: C. V. Mosby Company, 1949.

An Introduction to Gastro-Enterology. By Walter C. Alvarez, Professor of Medicine, University of Minnesota, The Mayo Foundation, and a Senior Consultant in the Division of Medicine, the Mayo Clinic. Fourth edition, revised and enlarged. Cloth. Price, $12.50. Pp. 903, with 269 illustrations. New York: Paul B. Hoeber, Inc., 1948.

Urological Aspects of Spinal Cord Injuries. By George C. Prather, M.D., Department of Genito-Urinary Surgery, Harvard Medical School, Boston, Massachusetts. Cloth. Price, $3.75. Pp. 146, with 42 illustrations. Springfield, Illinois: Charles C Thomas, 1949.

L'URÉTHROGRAPHIE. By R. Guichard, Radiologiste des Hôpitaux de Bordeaux, and H. Duvergey, Ancien Chef de Clinique Urologique à la Faculté de Bordeaux. Préface du Professeur Darget. Paper. Price, 650 fr. Pp. 190, with 175 illustrations. Paris: Masson et Cie., 1948.

LA CHIRURGIE BILIAIRE SOUS CONTRÔLE MANOMÉTRIQUE ET RADIOLOGIQUE PER-OPÉRATOIRE. By Pierre Mallet-Guy, Professeur à la Faculté de Médecine de Lyon, Chirurgien des Hôpitaux; René Jeanjean, Assistant à la Faculté, Ancien interne des Hôpitaux; and Pierre Marion, Chef de clinique à la Faculté, Ancien interne des Hôpitaux. Paper. Price, 1200 fr. Pp. 138, with 170 illustrations. Paris: Masson et Cie., 1947.

RADIOLOGIA SCHERMOGRAFICA, By Franco Fossati, L. D. di Radiologia nell'Univ. di Milano; and Patrizio Gallone, Dottore in Fisica. Cloth. Price, Lire 3000. Pp. 387, with 157 illustrations. Milano: Garzanti, 1949.

X-RAY TREATMENT: ITS ORIGIN, BIRTH AND EARLY HISTORY. By Émil H. Grubbé, B.S., M.D., F.A.C.P., Charter Member and Emeritus Member of the Radiological Society of North America; Charter Member of the American Roentgen Ray Society; etc. Cloth. Pp. 153, with 51 illustrations. St. Paul: The Bruce Publishing Company, 1949.

BILHARZIAL CANCER: RADIOLOGICAL DIAGNOSIS AND TREATMENT. By Mahmoud Ahmed Afifi, M.B., Ch.B. (Cairo), M.R.C.S. (England), L.R.C.P. (London), D.M.R.E. (Cambridge), Former Director of the Radiological and Electro-therapeutic Departments of the Egyptian Government Hospital, Alexandria. Cloth. Price, 16/. Pp. 111, with 60 illustrations. London: H. K. Lewis & Co., Ltd., 1948.

RADIOTHERAPY AND CANCER. By A. G. C. Taylor, M.R.C.S., L.R.C.P., D.R., F.F.R., Chief Radiotherapist; Joan Lassetter, M.C., Ch.B., D.R., Royal Victoria and West Hants Hospital, Bournemouth; and T. K. Morgan, M.B., M.R.C.S., D.M.R. (T.), Royal South Hants and Southampton Hospital. Cardboard. Price, 7s. 6d. Pp. 81. London: H. K. Lewis & Co., Ltd., 1948.

ALLGEMEINE STRAHLENTHERAPIE—LICHT, RÖNTGENSTRAHLEN, RADIUM. By Prof. Dr. Otto Jüngling. Edited by Doz. Dr. R. Glauner and Prof. Dr. H. Langendorff. Second edition. Cardboard. Price, DM 29.50 bound. Pp. 354, with 145 illustrations. Stuttgart: Ferdinand Enke.

DIE INDIKATIONEN ZUR RÖNTGEN- UND RADIUMBESTRAHLUNG. By Dr. Med. Habil. R. Glauner, Dozent für Röntgenologie und Strahlenheilkunde, Stuttgart. Paper. Price, $2.25. Pp. 124, with several tables. Stuttgart: Georg Thieme, 1948.

DAS ADENOCARCINOM DES COLLUM UTERI—HISTOLOGISCHE, KLINISCHE UND THERAPEUTISCHE ERGEBNISSE. By Dozent Dr. Hans Limburg and Dr. Klaus Thomsen. Paper. Price, DM 6.80. Pp. 87, with 39 illustrations. Stuttgart: Georg Thieme, 1949.

THE 1949 YEAR BOOK OF RADIOLOGY—(June, 1948–June, 1949). Radiologic Diagnosis edited by Fred Jenner Hodges, M.D., Professor and Chairman, Department of Roentgenology, University of Michigan; and John Floyd Holt, M.D., Associate Professor, Department of Roentgenology, University of Michigan. Radiation Therapy edited by Isadore Lampe, M.D., Associate Professor, Department of Roentgenology, University of Michigan. Cloth. Price, $6.50. Pp. 453, with 393 illustrations. Chicago: Year Book Publishers, Inc., 1949.

STANDARD RADIOGRAPHIC POSITIONS. By Nancy Davies, M.S.R., C.T., Senior Radiographer, Malvern General Hospital, Malvern, etc., and Ursel Isenburg, M.S.R., Radiographer, Royal Free Hospital, London, etc. Second edition. Cloth. Price, $6.00. Pp. 223, with 384 illustrations. Baltimore: Williams & Wilkins Company, 1948.

CONFRONTATIONS—RADIO-ANATOMO-CLINIQUES. Published under the direction of M. Chiray, R. A. Gutmann, and J. Sénèque. Volume II. Paper. Price, 465 fr. Pp. 67, with 140 illustrations. Paris: G. Doin et Cie., Masson et Cie., 1947.

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Précis de Technique Radiographique. By P. Porcher. Médecin Radiologiste de l' Hôpital Saint-Antoine et de l'Hôpital Américain. Second edition, completely revised. Ouvrage Couronné par l'Académie des Sciences (Prix Montyon 1939, Mention honorable). Cloth. Price, 3500 fr. Pp. 508, with 431 illustrations. Paris: Gauthier Villars, 1948.

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Isotopic Tracers and Nuclear Radiations with Applications to Biology and Medicine. By William E. Siri. Contributions by Ellsworth C. Dougherty, Cornelius A. Tobias, Rayburn W. Dunn, James S. Robertson, and Patricia P. Weymouth—Division of Medical Physics. Department of Physics and Radiation Laboratory, University of California. Cloth. Price, $12.50. Pp. 653, with 136 illustrations and 49 tables. New York: McGraw-Hill Book Co., Inc., 1949.

Biological Reactions Caused by Electric Currents and by X-rays: A theoretical study of the phenomena of excitation in the nerve by different electric currents and of the biological reactions caused by X-rays, both based upon a common principle. By J. Th. van der Werff, M.D., D.Sc. Cloth. Price, $5.00. Pp. 203, with 38 illustrations. New York: Elsevier Publishing Co., Inc., 1948.

Über die neuen Strahlenschutzregeln für die Herstellung und Errichtung medizinischer Röntgeneinrichtungen und -anlagen DIN 6811 und 6812. By Dipl.-Ing. Herbert Graf, Oberingenieur der Siemens-Reiniger-Werke A. G., Erlangen. Paper. Price, $1.25. Pp. 72, with several tables. Stuttgart: Georg Thieme, 1949.

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ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M. D., Harper Hospital, Detroit 1, Michigan

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

Abdomen

Lorber, S. H., and Machella, T. E.: Enteric cyst of the duodenum 275
Edwards, M.: Four metachronous malignant lesions of the colon 275
Weinberger, H. A., and Paltauf, R. M.: Tumors of the small intestine 276
Eckel, J. H.: Primary tumors of the jejunum and ileum 276
D'Albora, J. B., and Ingegno, A. P.: Carcinoid tumors of the small bowel 277
Gottlieb, C., Sharlin, H. S., and Peck, W.: Roentgen finding of unusual interest in perforation of the colon 277
Lindberg, G., and Morales, O.: Treatment of acute intussusception by an enema of roentgenologic contrast medium 277
Habibi, M.: Relation of the tumor and pseudotumor processes to amebic dysentery 278
Hoxworth, P. I., and Slaughter, D. P.: Polyposis of the colon 278
Moore, G. E., and Smith, M. J.: Intravenous cholecystography with tetraidophthalic fluorescein 279

Genitourinary System

Piccolo, G., and Longo, G.: Concerning pyelorenal reflux 279
Marshall, V. F., and Schnittman, M.: Iliac lymphadenopathy as a cause of ureteral obstruction 280
Obrinsky, W.: Agenesis of abdominal muscles with associated malformation of the genitourinary tract 280
Hickel, R., and Cornet, P.: Roentgen signs of polycystic disease of the kidneys 280
Mertz, H. O., Hendricks, J. W., and Garrett, R. A.: Cystic ureterovesical protrusion 280
Watson, E. M., Sauer, H. R., and Sadugor, M. G.: Manifestations of the lymphoblastomas in the genito-urinary tract 281
Gahagan, H. Q., and Fischmann, J. L.: Carcinoma of the prostate 281

Skeletal System

Dale, J. H.: Leukemia in childhood 281
Sear, H. R.: Engelmann's disease 282
Pinkus, H., *et al.*: Reticulogranuloma 282
Christie, A.: Prevalence and distribution of ossification centers in the newborn infant 282
Poulhès, J.: Ossification centers of the lower extremity in infants prior to two years of age 283

General

Garland, L. H.: On the scientific evaluation of diagnostic procedures 283

ROENTGEN AND RADIUM THERAPY

Barnett, J. C., Polisar, I. A., and Polisar, R. S.: Use of a plastic tracheal cannula, with report of a case 284
del Regato, J. A.: Roentgen therapy of carcinoma of the skin of the eyelids 285
Lauge-Hansen, N., and Lyndrup, S.: Hidrosadenitis axillaris and its roentgen treatment (optimum total dose and intenseness) 285
Daland, E. M.: Radiation necrosis of the jaw 285
Leddy, E. T., and Maytum, C. K.: Roentgen treatment of bronchial asthma 286
Read, J. M.: Graves' disease 286
Shullenberger, C. C., Watkins, C. H., and Kierland, R. R.: Experiences with nitrogen mustard therapy 287
Bouslog, J. S.: Roentgen irradiation of thrombophlebitis 287
Payson, B. A., and Rosh, Rieva: Carcinoma and other neoplasms of the male breast .. 287
Treves, N.: Castration as a therapeutic measure in cancer of the male breast 288
Kaae, S.: Testosterone propionate in the treatment of breast cancer 288
Habibi, M.: Two cases of cancer of the breast in two young girls, one seven and the other nine years old 289
Gricouroff, G.: Histopathologic prognosis of cancer of the breast 289
Gordon-Taylor, G., McWhirter, R., and Cade, S.: Treatment of cancer of the breast 289
Lowenhaupt, Elizabeth, and Steinbach, H. L.: Clinical response of metastatic lesions of carcinoma of the female breast to hormonal therapy as related to histologic grade of malignancy 290

Ernst, E. C.: Probable trends in the irradiation treatment of carcinoma of the cervix uteri with the improved expanding type of radium applicator..... 290
Waterman, G. W., and Reid, W. A.: Place of deep external x-ray irradiation in the treatment of carcinoma of the cervix by long element needles..... 290
Bowing, H. H.: Immediate and late results of intracavitary radium therapy for malignant lesions of the cervix..... 291
Twombly, G. H., and Chamberlin, J. A.: Intravaginal roentgen therapy in cancer of the cervix uteri..... 291
Caulk, R. M.: Review of ten years experience with transvaginal roentgen therapy..... 292
Buschke, F., and Cantril, S.: Roentgen therapy of benign giant-cell tumors of bone.. 292
Pendergrass, E. P., and Kirsh, D.: Role of irradiation in the management of carcinoma of the breast..... 293
Costolow, W. E.: Carcinoma of the cervical stump..... 294
Mullenix, R. B., and Prentiss, J. R.: Critical analysis of treatment of bladder tumors..... 294

RADIOISOTOPES

Stanley, M. M., and Astwood, E. B.: Response of the thyroid gland in normal human subjects to the administration of thyrotropin, as shown by studies with I^{131}..... 294
Werner, S. C., Quimby, Edith H., and Schmidt, Charlotte: Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine (eight-day half-life)..... 294
Rawson, R. W., and Skanse, B. N.: Radioactive iodine..... 295
Chapman, E. M., Skanse, B. N., and Evans, R. D.: Treatment of hyperthyroidism with radioactive iodine..... 295
Frantz, Virginia K., Quimby, Edith H., and Evans, T. C.: Radioactive iodine studies of functional thyroid carcinoma..... 296
Marinelli, L. D., *et al.*: Factors involved in the experimental therapy of metastatic thyroid cancer with I^{131}..... 296

MISCELLANEOUS

Taylor, H. K.: Apparatus for automatic multiple exposures..... 297
Chapman, D. W., Gugle, L. J., and Wheeler, P. W.: Experimental pulmonary infarction..... 297
Leblond, C. P., Gross, J. Thyroglobulin formation in the thyroid follicle visualized by the "coated autograph" technique..... 298
Bocchi, E.: Concerning the search for a vagus substance liberated from the sectioned end of an irradiated nerve..... 298
Goldfeder, Anna: Further studies on the radiosensitivity of tumors autogenous to homozygous hosts..... 298

ROENTGEN DIAGNOSIS

ABDOMEN

Lorber, Stanley H., and Machella, Thomas E. Enteric cyst of the duodenum. *Gastroenterology*, May, 1948, *10*, 892–899.

An enteric cyst of the duodenum is reported and the literature on such tumors is reviewed.

The roentgenological examination after barium meal revealed a probable tumor of the second portion of the duodenum. To establish the diagnosis a technique used by the authors and described by Shiffer was employed. The third portion of the duodenum was intubated with a double lumened Miller-Abbott tube, one lumen of which communicated with a distally placed balloon capable of holding 50 cc. of air. Inflation of the balloon in the lower duodenum produced pain similar to that about which the patient had previously complained. A barium suspension was injected through the other lumen of the tube into the section of the duodenum proximal to the balloon. The tumor was clearly delineated in the second portion of the duodenum by this method.—*Franz J. Lust, M.D.*

Edwards, Monte. Four metachronous malignant lesions of the colon. *Surgery*, May, 1948, *23*, 808–813.

The author reports an interesting case of a physician who had 4 separate carcinomas of the colon resected between 1927 and 1946. Three of these tumors were undoubtedly primary while the fourth, which arose at the site of previous resection in the right portion of the transverse colon, may have been a recurrence. Although a statement is not made as to the microscopic grade of these adenocarcinomas, the photomicrographs clearly show well defined glandular arrangements of the malignant epithelial cells. The patient was apparently living and practicing his profession in 1947 and had outlived two of his surgeons. The unusual fea-

ture is the apparent absence of polyposis preceding these lesions. Reproductions of roentgenograms showing 2 lesions are presented.—*C. B. Holman, M.D.*

WEINBERGER, H. A., and PALTAUF, R. M. Tumors of the small intestine. *Surgery*, July, 1948, *24*, 35–53.

The authors report on 19 of 20 cases of tumor of the small bowel and include a review of some of the more comprehensive studies in the literature. These tumors are uncommon. There was 1 to every 71 other gastrointestinal neoplasms in the authors' experience. There were 13 malignant and 6 benign tumors in this group which included patients from thirty-five to seventy-nine years of age.

The average duration of symptoms in cases of malignant lesions was ten months. No symptoms or signs of specific diagnostic value could be determined. Eleven patients had lost some weight, 9 had vague periumbilical, intermittent aching pain, 7 had intestinal obstruction, 5 had palpable masses and 4 had symptoms of bleeding. Of patients with benign lesions 4 had pain in the lower quadrant, 3 had diarrhea or constipation, 3 had intestinal obstruction, 3 had palpable masses and 1 had had bleeding.

Roentgenoscopic and roentgenographic studies were carried out in 7 cases in which the patients had malignant lesions and in 3 of which the lesions were benign. Of the former 7 cases intestinal obstruction was observed in 4, a diagnosis of neoplasm was made in 1 and filling defects were reported in 2. In the latter 3 cases, 1 was negative, 1 showed mechanical obstruction and 1 showed a filling defect. Although less satisfactory than examination of either the stomach or colon, the authors urge that examination of the small bowel be undertaken if the patient's complaints are bizarre, especially when there is bleeding which is not satisfactorily explained. The interpretation of filling defects, changes in contour, localized paralysis and changes of intraluminal diameter must be left to the trained radiologist. In a few instances a dilated, smooth aneurysmal-like sac corresponding to the segment paralyzed by malignant infiltration is found which is almost pathognomonic of lymphosarcoma.

Data concerning the pathology of the lesions are summarized in a table. The majority of the lesions were located near the beginning or the end of the small intestine. Three of 13 malignant and 4 of 7 benign lesions were associated with intussusception. In the duodenum there were 3 adenocarcinomas and 1 melanosarcoma; in the jejunum there were 3 carcinomas, 1 leiomyosarcoma and 1 polyp; in the ileum there were 1 carcinoma, 1 lymphosarcoma, 1 spindle-cell sarcoma, 1 leiomyosarcoma, 4 fibromas, 4 lipomas and 1 leiomyoma. In all cases of adenocarcinoma metastasis was present. All sarcomas were fairly well circumscribed and partially encapsulated. Of 10 patients having malignant lesions who were operated on, 2 were living and well at the time this report was written. The diagnosis in these 2 cases was leiomyosarcoma.

The authors agree with others in that tumors of the small bowel do not cause any diagnostic symptom complex, that the roentgenologic study may be inconclusive and that laparotomy should be advised more frequently when exhaustive diagnostic studies leave doubt.—*C. B. Holman, M.D.*

ECKEL, JOHN H. Primary tumors of the jejunum and ileum. *Surgery*, March, 1948, *23*, 467–475.

A brief summary of the literature is followed by a report of the author's experience at the New York Hospital since September 1, 1932, where 19 cases of primary tumor of the jejunum and ileum have been histopathologically established.

Twelve lesions were malignant and 7 were benign. Three of the latter represented incidental findings at necropsy. Eight of the patients having malignant lesions were males and 4 were females. Cramping abdominal pain, usually mild or vague at onset, was the earliest symptom of all but 1 patient. The other important symptoms were loss of weight, vomiting and constipation. All presented weakness and fatigue and 6 gave histories of melena. A palpable abdominal mass and some abdominal distention were the most important physical signs. One patient had general peritonitis and high obstruction. Two-thirds of the patients had anemia and occult blood in the stools. Tumors were found by roentgenologic examination in 9 cases, the chief signs being a split in the barium stream, narrowing of the lumen and retention of barium in cases in which the patient had some obstruction.

The treatment of choice is resection with end-to-end anastomosis. Postoperative roentgen therapy should be used when the diagnosis is

lymphosarcoma whether or not resection has been accomplished.

There were 10 jejunal and 2 ileal malignant tumors, the proximal jejunum being the commonest location. These included 6 adenocarcinomas, 4 lymphosarcomas, 1 leiomyosarcoma which perforated and 1 carcinoid with metastasis. Intussusception was present in 2 cases. Five of the 8 patients with resectable lesions survived. The long interval between onset of symptoms and diagnosis resulted in less favorable prognosis.

Of the benign lesions 4 were leiomyomas and 1 was a polyp, 1 a lipoma and 1 a fibroma. Four of these lesions produced symptoms which were similar to those of malignant lesions, but there were no abdominal masses. In 3 cases roentgenologic examination revealed evidence of obstruction or tumor. Complete tables summarize the important clinical features and course in each case. The importance of careful exploration of the small intestine in the presence of these clinical features is emphasized.—*C. B. Holman, M.D.*

D'Albora, John B., and Ingegno, Alfred P. Carcinoid tumors of the small bowel. *Gastroenterology*, Feb., 1948, *10*, 310–326.

Four instances of operatively demonstrated small intestinal carcinoid are reported. All were in the ileum. Two had caused intestinal obstruction. One had produced metastatic tumefaction of mesenteric nodes discovered on routine examination. The fourth case was an unusual combination of symptomatic Meckel's diverticulum and carcinoid, the latter being an incidental finding. The difficulties of diagnosis are emphasized by the fact that the nature of the lesion was not suspected preoperatively in spite of careful study. Carcinoids of the small bowel are unusual but constitute a relatively high proportion of symptomatic small intestinal tumors. A résumé of their origin, character, and symptomatology is given. Their presence should be particularly suspected in middle-aged or elderly individuals with a long-standing history of digestive disturbance and episodes suggesting partial intestinal obstruction. Surgical resection, even in the presence of metastasis, is the treatment of choice and the prognosis is relatively good. Three of the patients are alive ten, sixteen and seventy-five months after operation. —*Franz J. Lust M.D.*

Gottlieb, Charles, Sharlin, Herbert S., and Peck, William. A roentgen finding of unusual interest in perforation of the colon. *Radiology*, March, 1949, *52*, 359–362.

The authors present 2 cases of perforation in the colon in which films had been obtained prior to death. In each case the fecal material could be visualized in the abdomen, not conforming to the expected outline of the colon.

Free air could not be demonstrated except as it gave a mottled appearance to the free fecal matter in the abdomen. The localization of the matter aided in determining the site of perforation.—*Vernon L. Peterson, M.D.*

Lindberg, Gustaf, and Morales, Olallo. Treatment of acute intussusception by an enema of roentgenologic contrast medium. *Am. J. Dis. Child.*, March, 1949, *77*, 303–309.

The conservative treatment of intussusception in children has been a subject of interest for many years in the Scandinavian countries. This paper is based on 18 cases in children under the age of three years, all of whom were treated conservatively by means of contrast medium with successful results. The favorable results seemed to depend mainly on two factors: the short time which elapsed before treatment, in most cases only a few hours, and the technique used in the administration of the reducing enemas.

The authors emphasize the correct temperature and consistency of the medium and also the pressure used. The enema is poured from a position about 5 feet above the level of the patient. No alkali or other material to render the mixture smoother is added to the mixture. Pharmabaryt, 1 kg. is mixed with 1.25 liter water at a temperature of 37° C. (98.6° F.). The medium is allowed to flow until the obstruction is reached and a roentgenogram of the intussusception is then taken. The colon is then slowly filled and the intussusception is pushed in an oral direction. The colon is usually irritated and contracts in cramp, thereby pushing back the contrast medium and practically emptying the intestine. It is important to cut off the flow of the enema until the contraction has ceased, when it can be renewed. Sometimes it appears as though the oral movement has ceased as a result of the contraction of the outer tube, and it is best to pause until the intestine

has relaxed. As far as possible, manual pressure should be avoided since this tends to increase the irritation of the colon. With this procedure, it is usually possible to press out the intussusception to the region of Bauhin's valve and even to reduce it altogether. Reduction may be considered complete only when the contrast medium passes freely on into the small intestine. Unfortunately, it frequently happens that a part of the obstruction about the size of a walnut remains in the cecum which one is forced to remove manually. This is done by holding the movable cecum with one hand while massaging in an oral direction with the other. This procedure may be continued for about fifteen minutes. Should it not succeed, a pause of ten to fifteen minutes is advised to allow both the patient and the colon to relax. A renewed attempt then should prove successful. The intussusception can be seen to disappear as shown by a sudden jerk of the medium as it flows out into the small intestine. Patients in whom, even with the help of a narcotic, positive results have not been obtained will have to be treated surgically. No complication as a result of the enema treatment has been observed at subsequent operations.

The authors think their results depend upon several factors. All cases are not reducible by this method. Especially responsive to this treatment are those arising at the boundary between the small intestine and the colon and their series consisted only of such cases. Furthermore, the time elapsed after the onset of symptoms in 5 cases was one to two hours, in 3 cases three hours, in 6 cases four to six hours, and in 4 cases eight to twelve hours. Other factors contributing to their favorable results are the technique employed in the attempts at reduction and the use of narcotics in the cases otherwise resistant to reduction. In 3 of 18 cases reduction was impossible without the use of general anesthesia. They have encountered no cases of rupture of the intestine. It is obvious, they believe, that the pressure of the contrast medium is proportionately greater the younger the child, and the intestine of a young child is more responsive to the manipulation necessary in attempts at reduction.—*R. S. Bromer, M.D.*

Habibi, M. Processus tumoreux et pseudo-tumoreux en relation avec la dysenterie amibienne. (Relation of the tumor and pseudo-tumor processes to amebic dysentery.) *Bull. Assoc. franç. l'étude cancer*, 1947, *34*, 65–74.

The author presents 3 cases, and the following conclusions concerning his investigations:

1. Amebic dysentery can sometimes provoke hyperplastic and tumorous reactions. These may be benign, malignant, or hyperplastic in type.

2. Certain authors explain the simultaneous presence of a malignant tumor and an amebic infection, as the result of a maligant transformation of the amebic lesion. However, the author believes that that explanation does not correspond with the facts. He believes that there is simply a coincidental occurrence of both lesions rather than a malignant transformation of the amebic lesions. He makes this suggestion because in spite of the frequency of amebic dysentery, and cancer of the rectum in Iran, he was unable to find the coexistence of a case of cancer with amebic colitis.

3. The inflammatory and hyperplastic lesions of amebic dysentery sometimes produce tumors of the intestinal wall, giving the macroscopic appearance of a cancer. Not only does the exterior aspect of these pseudo-tumors of amebic lesions give the appearance of a cancer but also their clinical manifestations, their evolution, their roentgen signs, and their proctoscopic aspects simulate malignancy.

4. In a patient with a tumor of the colon, rectum, or of the cecum, one must suspect an amebic affection, especially when one lives in a country where that disease is endemic.

In order to made a correct diagnosis, one should make a careful study for amebae and also perform a biopsy.

Six figures illustrate the article.—*Panagiotis S. Nemfakos, M.D.*

Hoxworth, P. I., and Slaughter, D. P. Polyposis of the colon. *Surgery*, July, 1948, *24*, 188–211.

This article presents a historical review of the condition known variously as "polyposis (adenomatosis)," "disseminated polypi," "multiple adenomas," "multiple polypi," "multiple papillomata," "multiple adenomatosis" and "multiple polyposis."

In 1930 Dukes' classic review of the subject was published. He commented on the terminology and favored the designation "polyposis." Polyposis and polypi secondary to inflamma-

tion were confused in the earlier descriptions as recognized by Woodward in 1881. Today some doubt occasionally exists in cases of inflammatory conditions of long standing. Laschka, in 1861, presented a convincing description of the disease in the case of a woman thirty years of age. Distinction also must be drawn between this condition and that of polyps occurring singly or in small numbers. The differentiation from "the more frequent occurence of isolated polyps, cancer, and inflammatory diseases of the colon and rectum . . . " depends on " . . . a careful history, stool examinations, sigmoidoscopy, and roentgenologic study after barium and air enemas."

Cripps, in 1882, recognized the familial and congenital characteristics of polyposis of the colon in reporting 2 cases. The authors regard polyposis as "an example of gene mutation transmitted by both sexes, and appearing in succeeding generations as Mendelian dominants or recessives." The age at which the peak of incidence occurs is about thirty years. The well known frequent association of this disease with malignant change was first emphasized by Hansen in 1895.

The authors present reports of 7 cases together with summaries making a total of 35 cases in the American literature. The cases show considerable variation in the sequence of surgical procedures. Total removal of the large bowel with external ileostomy or with ileosigmoidostomy (or ileoproctostomy) with fulguration of the lower segment were the only methods which resulted in permanent cure. In each case the method, extent and sequence of the operative procedures depended on the patient. Factors favoring total ablation and those favoring preservation of the sphincter are tabulated.—*C. B. Holman, M.D.*

Moore, G. E., and Smith, M. J. Intravenous cholecystography with tetraiidophthalic fluorescein. *Surgery*, July, 1948, *24*, 17–21.

The intravenous use of sodium tetraiodophthalic fluorescein in cholecystography is described. The method is of advantage when the variable factor of intestinal absorption is to be circumvented and when it is desired to shorten the time interval in visualizing the gallbladder.

The drug is prepared by substituting iodine in the phthalic ring. It contains 57.7 per cent iodine. Iodine may be substituted in the fluorescein component but this results in a less soluble, more toxic compound which stains the patient's skin a deep cherry red.

Forty milligrams of the dye per kilogram of body weight in 15 cc. of solution is administered intravenously during a period of one to two minutes. The first roentgenogram is made two hours after injection of the drug. A fatty meal is then given and another roentgenogram is made forty minutes later. If a poor shadow is obtained an additional roentgenogram is made in three hours. The only preparation necessary is a light fat-free breakfast.

The interval of two to three hours between administration of the drug and the first roentgenographic exposure was selected as a result of studies made with a similar dye in which radioactive iodine was substituted. Forty-five minutes after injection there was a marked increase in counts made with a Geiger counter over the gallbladder area.

Twenty-two patients were examined by this method. Results were (1) good visualization of the gallbladder in a majority, (2) nonvisualization of the gallbladders of 4 patients, 2 of whom were operated on and found to have pathologic gallbladders; (3) nonvisualization of the common duct of a patient whose gallbladder had been removed. The skin of all patients was tinted a light flesh pink which remained visable for several hours.—*C. B. Holman, M.D.*

GENITOURINARY SYSTEM

Piccolo, Giacinto, and Longo, Giuseppe. Sui reflussi pielo-renali; contributo sperimentale. (Concerning pyelorenal reflux; experimental contribution.) *Radiol. sperimentale*, Jan.–Feb. 1948, *2*, 68–79.

The question of the degree of intrapelvic pressure necessary for pyelorenal backflow is controversial. Some authors maintain that an indispensable factor is the increase of intrapelvic pressure with respect to the secretory pressure of the kidneys. Others affirm that this phenomenon can occur also with intrapelvic pressure equal or less than the secretory pressure.

The authors conducted experiments on pyelorenal reflux in dogs. They first determined the normal secretory pressure; then they determined the pressure resulting from the injection of diuretics and contrast media. In a second group of experiments followed by means of retrograde pyelography, they determined the minimum pressure necessary to bring about a

pyelorenal reflux and concluded that the secretory pressure in dogs varies between 50 and 70 mm. of water and that the retrograde pressure necessary to cause a reflux greatly exceeds the normal secretory pressure.—*Lucien M. Pascucci, M.D.*

MARSHALL, V. F., and SCHNITTMAN, M. Iliac lymphadenopathy as a cause of ureteral obstruction. *Surgery*, March, 1948, *23*, 542–549.

The authors describe a diagnostic pattern whereby a reasonable assumption may be made that ureteral obstruction is due to iliac lymphadenopathy, although this cause has heretofore received little emphasis.

The diagnostic features are as follows: (1) pain in the flank without significant urinary symptoms; (2) a hydronephrotic or nonfunctioning kidney (by intravenous pyelography) present on the involved side; (3) ureteral constriction consistently present at the pelvic brim and invariably located 9 to 10 cm. above the ureteral orifice; (4) normal ureter below the point of constriction, and (5) the length of the constricted segment never more than 3 mm., usually only 1 mm. The constricted segment is demonstrated by intravenous urograms for the ureter above the constriction (when the kidney shows function) and by means of the retrograde instillation of an opaque medium through a ureteral catheter for that portion below the obstruction. Other causes of ureteral obstruction at this level, such as calculus or primary ureteral neoplasm, are excluded by careful urologic survey. The history will exclude traumatic stricture and pregnancy. An iliac aneurysm usually shows the presence of calcium in its wall, and congenital valves, folds and aberrant vessels are usually manifest at an early age and are rarely at this level. Idiopathic stricture is stated to be less sharply demarcated and is usually chronic in nature. Obstruction was acute in the cases presented. Tuberculous ureteritis may resemble this condition, but the involved region is usually several centimeters long. Four proved cases and one without operation illustrating malignant iliac lymphadenopathy are reported.—*C. B. Holman, M.D.*

OBRINSKY, WILLIAM, Agenesis of abdominal muscles with associated malformation of the genitourinary tract. *Am. J. Dis. Child.*, March, 1949, *77*, 362–373.

The congenital absence of the anterior and lateral abdominal musculature is a rare anomaly that merits additional description in this report because of its simultaneous occurrence with certain malformations of the genitourinary tract. These malformations include an enlarged and hypertonic bladder, usually occupying an abdominal or fetal position, hydroureter, destruction or cystic degeneration of the renal parenchyma, with dilatation of the renal pelves and calyces, and cryptochism. A case with this combination of congenital anonalies is described in this paper.

Several theories concerning the origin of the syndrome are discussed. The author states that the argument may be put forward that since congenital obstructive hydronephrosis never causes muscular agenesis and since in the syndrome no organic obstruction was observed, the muscular agensis is the initiating force in the changes in the urinary tract. The agenesis operates by causing incomplete emptying of the bladder, leading to the adynamic type of hydronephrosis.—*R. S. Bromer, M.D.*

HICKEL, RICHARD, and CORNET, PAUL. Les signes radiologiques de la maladie polykystique des reins. (The roentgen signs of polycystic disease of the kidneys.) *J. de radiol. et d'électrol.*, No. 3–4, 1949, *30*, 113–124.

The many beautiful illustrations in this article almost comprise a roentgenologic atlas of this disease. A résumé of the authors' conculsions is as follows: The frequency of polycystic disease is greater than is generally believed; the diagnosis of this condition can be easy, difficult or impossible to establish. In the category of "difficult cases," the knowledge of the roentgen signs of polycystic disease of the kidneys can markedly augment the number correctly diagnosed. In the very difficult cases diagnosis may only be established at operation. In doubtful cases, recourse to pararenal air insufflation may be necessary.—*William M. Loehr, M.D.*

MERTZ, H. O., HENDRICKS, J. W., and GARRETT, R. A. Cystic ureterovesical protrusion; report of four cases in children. *J. Urol.*, March, 1949, *61*, 506–516.

The authors differentiate congential cystic ureterovesical protrusion from cystocele by the absence of a demonstrable ureteral orifice in the cystic dilatation of the former. The literature is summarized and the authors add 6 cases.

The etiology is presumably congenital. The diagnosis is made cystoscopically. The authors discuss a diagnostic test devised by one of them. This consists in injecting some radiopaque substance into the cyst through a needle which has been introduced per bladder. The needle is previously tied to and sealed into the end of a ureteral catheter. The 6 cases with illustrative films are discussed in detail.—*Rolfe M. Harvey, M.D.*

Watson, E. M., Sauer, H. R., and Sadugor, M. G. Manifestations of the lymphoblastomas in the genito-urinary tract., *J. Urol.*, March, 1949, *61*, 626–645.

Many cases of lymphoblastomatous involvement of the genito-urinary tract are probably asymptomatic and not recognized. This is proved by the high incidence of such involvement reported at postmortem examination (60–70 per cent) and the relatively low clinical incidence of involvement. The authors reviewed a series of 1,073 cases of lymphoblastoma and found a clinical incidence of urinary tract involvement of 7.3 per cent. The highest involvement was in leukemia and the lowest in Hodgkin's disease.

Bleeding was the most common evidence of involvement of the genito-urinary tract by lymphoblastoma and occurred in 7.5 per cent of cases with urological complaints. The kidney was involved in 82.5 per cent of the 80 cases studied with such complaints. Among positive kidney findings were displacement of the kidney, invasion of the renal parenchyma, direct extension from retroperitoneal nodes, gross multiple nodular infiltration of the parenchyma, and microscopic infiltration.

Commonly the kidneys or ureters may be displaced by adjacent extrarenal lymphoblastomatous masses. Involvement of the bladder is rare. Prostatic involvement leads to urinary obstruction. Testicular involvement is rare.—*Rolfe M. Harvey, M.D.*

Gahagan, H. Q., and Fischman, J. L. Carcinoma of the prostate; statistical study and evaluation of endocrine therapy, with a preliminary report on an additional method of treatment. *J. Urol.*, March, 1949, *61*, 587–590.

The authors have treated 118 patients with prostatic cancer by orchiectomy and 106 cases with stilbestrol. In order to compare their results they have used as a control 795 cases of prostatic cancer treated by other means than endocrine therapy.

The average survival age for the endocrine group from the time of diagnosis to death was 26.3 months as compared with 21.2 months for the non-endocrine group. The survival rate for the orchiectomy group was better than for the stilbestrol group.

In a few selected cases that had not responded to orchiectomy or stilbestrol roentgen irradiation of the adrenals was tried in the hope of eliminating any androgenic function these glands might have assumed. In 3 of the 10 cases so treated marked palliation was obtained.—*Rolfe M. Harvey, M.D.*

SKELETAL SYSTEM

Dale, J. H. Leukemia in childhood. *J. Pediat.*, April, 1949, *34*, 421–432.

This paper is based on a series of 72 cases of leukemia seen in the New York Hospital from 1932 to 1948. This was an incidence of 0.42 per cent of all pediatric admissions, and was the most frequently encountered malignant condition. The majority of cases occurred in the first five years of life. Ninety per cent of patients died within one year from the onset of symptoms; 95.8 per cent of the patients had acute leukemia, and two-thirds of these cases were of the lymphoid variety. Among characteristic symptoms were pallor, hemorrhagic manifestations, bone and joint pain and enlarged lymph nodes. Osseous lesions were found in 72.5 per cent of cases in whom the long bones were examined. Of this group 93.1 per cent had transverse radiolucent lines at the metaphyses, 41 per cent had osteolytic lesions and 24 per cent had periosteal elevation. No cases showed osteosclerosis, which has been described by others.

The band of metaphyseal rarefaction was found in areas of most rapid growth, appeared to be reversible in character, and the authors feel it is nonspecific and due to interference with endochondral bone formation. The osteolytic lesions were never found without one of the other two types of lesions and in autopsied cases leukemic cells were found in the lytic areas. The incidence of osseous changes increased with the duration of the disease. All cases with osseous changes showed lesions at the knee joint.

The authors call attention to the frequency with which rheumatic fever is diagnosed erroneously in leukemia cases.

In conclusion, roentgen examination of the knee joint is recommended as a useful screening device in suspected leukemia cases.—*Rolfe M. Harvey, M.D.*

SEAR, H. R. Engelmann's disease. *Brit. J. Radiol.*, May, 1948, *21*, 236–241.

A patient with Engelmann's disease, or osteopathia hyperostotica sclerotisans multiplex infantilis, the rarest of congenital bone dystrophies, is presented. The differential diagnosis, clinical, laboratory, and roentgenographic characteristics are given. A diagrammatic representation of the lesions peculiar to each of five congenital bone dystrophies is an aid in their differentiation.—*K. L. Krabbenhoft, M.D.*

PINKUS, HERMANN, COPPS, LYMAN, A., CUSTER, STANLEY, and EPSTEIN, STEPHAN. Reticulogranuloma; report of a case of eosinophilic granuloma of bone associated with nonlipid reticulosis of skin and oral mucosa under the clinical picture of Hand-Schüller-Christian disease. *Am. J. dis. Child.*, April, 1949, *77*, 503–519.

The case reported in this paper had bony lesions of eosinophilic granuloma which were associated with nonlipid cutaneous lesions such as are usually observed in Hand-Schüller-Christian disease and Letterer-Siwe disease.

The relationship of these diseases is discussed and the authors propose the term reticulogranuloma for the whole group. They suggest the following classification:

A. Reticulosis (Robb-Smith): Progressive hyperplasia of reticular tissue in lymph nodes or elsewhere without stromal destruction, as defined by Robb-Smith.

B. Reticulogranuloma: More or less discrete granulomatous lesions of various organs which infiltrate and destroy normal tissue in a manner similar to the infectious granulomas and which may heal without residue or more commonly, with fibrosis and scar formation. The predominant and characteristic cell form is the reticulum cell and its modifications: histiocytes, macrophages and foam cells.

1. Systemized, progressive type, exhibiting widespread involvement of various organs, having an acute or subacute course and usually resulting fatally (Letterer-Siwe disease, nonlipid reticulosis).

2. Lipid granulomatous type, with a chronic, usually progressive course and including cases which exhibit the Hand-Schüller-Christian syndrome, and others which do not, but in which xanthomatous transformation of the granulomas predominates. The osseous system is the site of predilection (lipid granuloma, Hand-Schüller-Christian disease).

3. Benign localized type with solitary or multiple lesions, usually restricted to bone, but occasionally involving the skin, exhibiting tissue eosinophilia and tending to heal spontaneously or with relatively simple treatment (e"osinophilic granuloma of bone" perhpas better designated as "benign rectiulogranuloma").

4. Mixed and transitional cases which combine features of two or all of the major types, either simultaneously or successively.

C. Reticulosarcoma (Oberling), malignant lymphoma (Gall and Mallory): True destructive blastomas which do not usually regress.

The authors do not intend this classification to be complete. It tries, however, to indicate the position of their case and similar cases in the large field of diseases of the reticuloendothelial system. Their case would have to be classified under 4 as a mixed form combining the features of 3 with cutaneous lesions as they are usually seen in 1 and 2.—*R. S. Bromer, M.D.*

CHRISTIE, AMOS. Prevalence and distribution of ossification centers in the newborn infant. *Am. J. Dis. Child.*, March, 1949, *77*, 355–361.

In two previous studies, it was conclusively demonstrated that race and sex are of the utmost importance in an appraisal of the osseous pattern of newborn infants. These studies were based on the presence or absence of the center for the cuboid bone. They revealed that this center was found to be present more frequently in Negro than in white infants of the same sex. In both races the center for the cuboid bone was found to be present more frequently in female than in male infants. The purpose of the present paper is to complete the observations for the presence or absence of each of nine other centers of ossification which may be visible in roentgenograms in the newborn infant, the weight at birth, race and sex being taken into consideration.

The study was based on 1,112 single-born newborn infants (298 white boys, 267 white girls, 271 Negro boys and 276 Negro girls). It would appear that the order of appearance of the centers is as follows: calcaneus, talus, distal epiphysis of the femur, proximal epiphysis of the tibia, cuboid bone, head of humerus, capita-

tum, hamate bone, third cuneiform bone and head of the femur. In general, all centers were found to be farther advanced in infants who were judged to be more mature when weight at birth was used as the criterion. On the whole, the Negro infants had a greater prevalence of any one center than the white infants. In general, the female infants had a greater prevalence of each center than the male infants in both races in the various weight groups.—*R. S. Bromer, M.D.*

Poulhès, J. Les noyaux d'ossification du membre inférieur chez l'enfant jusqu'a 2 ans. (The ossification centers of the lower extremity in infants prior to two years of age.) *J. de radiol. et d'électrol.*, No. 3–4, 1949, *30*, 124–126.

The results of this investigation by the author are taken from 2,500 cases studied by him. The author has handled his statistical study so that the normal date of appearance of an ossification center is taken by him to be that time when 50 per cent of the infants manifest the ossification center in question. The normal appearance of the principal ossification centers in the lower extremity, according to this author, are:

For the epiphysis of the femoral head..6 months
For the lower epiphysis of the femur...Before birth
For the upper epiphysis of the tibia....Before birth
For the lower epiphysis of the tibia....6 months
For the lower epiphysis of the fibula...1 year
For the cuboid.....1 month
For the 3rd cuneiform.....4 months

—*William M. Loehr, M.D.*

GENERAL

Garland, L. H. On the scientific evaluation of diagnostic procedures. *Radiology*, March, 1949, *52*, 309–328.

In investigation of the relative diagnostic efficiency of various techniques used in mass chest surveys, Birkelo, Chamberlain *et al.* found that experienced radiologists and chest specialists differed in their interpretation of films, not only from their colleagues (9–24 per cent), but also from themselves (3–31 per cent) on rereading of films. Three expert radiologists (C., R. and N.) made a similar study and found similar results, and thought it could be partially solved by simplifying the terminology. Although this reduced the intraindividual variation, it left the interindividual variation as large as before. Garland, in conjunction with Miller, Zwerling and Yerushalmy, undertook to more fully investigate this phenomenon—a phenomenon which at first glance appears unbelievable to each group of investigators studying it.

Actually, in every medical field that can be tested, there is a great variation in the consistency of clinical judgment and laboratory results. Radiology shares this expected variation but, if anything, to a lesser degree than other comparable procedures.

Garland's research committee divided the problem into three components:

I. *Seeing a Lesion.* Consistency in seeing a lesion is not sufficient, as the reader must also be consistently right; 399 films were read and reread by the GMZ group and there was 16 per cent interindividual, and 8.0 per cent intraindividual disagreement (i.e. totally contradictory).

To determine under- and overreading, the films were reviewed and classified as positive, negative and questionable. It was found that GMZ underread 7.0 per cent and overread 12 per cent. The underreading figure is lower than that for the CRN group, but is revised to 13 per cent when the questionable "inbetween group" is considered positive.

The reason for missing lesions was studied and only the early stages of the analysis presented. The group, as a whole, after reading the films separately, expressed group opinion as to why they thought a lesion easy or difficult of diagnosis. They found that, of the positive films which the group thought easy to diagnose, only 2.0 per cent had been called negative, of the "inbetween group" 14 per cent were missed, and of the difficult group, 33 per cent were missed. Of the negative films the ones thought easy of diagnosis were overread in 12 per cent, the "inbetween" in 23 per cent and the difficult in 27 per cent. It is thus clear that it is more difficult to read a negative than a positive film.

On the positive films three reasons were given for considering a film easy of diagnosis:

1. Location—upper part of lung or interspace;
2. Size—the larger lesions are easier;
3. Density—the greater the density, the easier the reading.

and difficult of diagonsis:

1. Location—hidden or merged with rib or heart shadow;
2. Density—faint shadows are more difficult;

3. Difficult of interpretation i.e. looks like vessel or artefact.

For the negative films, ease of diagnosis was essentially due to *good quality* of films, and difficulty of diagnosis to extraneous shadows or poor quality of films.

II. *Interpretation of Lesion.* This aspect was studied in one phase, i.e. the attitude of the reader.

The committee members reread the large group of films and the readers assigned to each probable lesion the "worst possible prognosis" (when in doubt, a film was read as positive). Actually only one reader followed these instructions and he missed none of the films called positive by the others, whereas the other two men did miss a few.

A method was therefore devised to utilize this "pessimistic" attitude. The reader separates the films into two piles, one definitely negative and the other containing the positives and questionables. Then he reviews the second pile critically. To test this method 225 films were studied twice by the readers; first, by separation into negatives and positives (or questionables), followed by critical review, and second, by the same method yet using a pessimistic attitude. By the first method, of the positive films 15.3 per cent were missed and by the second only 10 per cent.

In the study of overreading, it was found that by the first method, films considered negative were read as positive in 4.7 per cent and by the second method in 7.0 per cent. The overreading for the pessimistic method is not unduly greater.

III. *Describing a Lesion.* In the studies made by the CRN group it was found that the more categories or terms that were used in describing a lesion, the greater was the inconsistency among different readers, and for the same reader with himself. GMZ therefore tried out six terms for description, and their results show greater consistency than CRN, but the descriptions were admittedly too coarse to be clinically useful. The location was marked on the films. and the use of the following terms was studied; (1) shape, (2) orientation, (3) size, (4) density, (5) sharpness, and (6) uniformity.

The results of this study are given in a table and it is found that the degree of consistency is very low on most of the terms used. It is generally lower for interindividual than for intraindividual comparisons. The best score, 82.9 per cent, was attained for intraindividual comparisons on orientation; the worst, 51.1 percent, for interindividual comparisons on sharpness. Although these results are not good, they are better than those obtained using multiple categories.

A valuable result of these studies should be the renewed recognition of personal variability, which will make us more critical of our own work, and more tolerant in the appraisal of that of others.

Two methods are suggested for improving our accuracy of survey diagnosis:

1. Double reading by two observers. Theoretically, when an individual reader misses 20 per cent of the positives, a second reader will reduce the misses to about 4.0 per cent.

2. Review reading by a single observer.

It would appear that slow, careful reading would correct the errors, but this has not proved to be the case even with the experts. In general, the author recommends the following as a desirable "technique" for reading *survey films*:

1. A consistent method of reading each film. A satisfactory system for the chest is suggested as follows: heart-vessel shadow, lungs as a whole; then each lung space by space, then rib by rib from apex to base, with careful comparison of each side, and finally review of the bony thorax and soft tissues.

2. Avoidance of eyestrain. Take rest periods frequently.

3. Always attempt to "see" first and "interpret" secondly.

Suggestions are given by Garland for testing readers for survey work. He and the group plan further studies to clarify many of the problems which arose during the present analysis.—*M. E. Mottram, M.D.*

ROENTGEN AND RADIUM THERAPY

BARNETT, JAMES C., POLISAR, IRA A., and POLISAR, ROBERT S. Use of a plastic tracheal cannula, with report of a case. *Radiology*, March, 1949, *52*, 416–418.

The metal tracheotomy tube worn during the course of postoperative irradiation of the neck is customarily removed during deep roentgen therapy because of the dead-spot behind the tube and because of the tracheal epithelitis resulting from the secondary and characteristic radiation. Remvoal of the tube is a source of discomfort to the patient.

The authors constructed a tracheal cannula

of non-toxic plastic, which is non-irritating to the tracheal epithelium and which can be left in situ throughout the course of therapy. The absorption of radiation is equivalent to that of soft tissue or water (5.5 per cent). The metal obturator can be used when necessary and is easily removed. A case is presented using this device.—*Gabriel Whiteman, M.D.*

DEL REGATO, J. A. Roentgen therapy of carcinoma of the skin of the eyelids. *Radiology*, April, 1949, *52*, 564–573.

The author reports on 168 consecutive cases of carcinoma of the skin of the eyelids and of the inner and outer canthi, which have been followed for a minimum of three years. The patients ranged in age from thirty-five to eighty-nine years, the median age being seventy years. The lesion was considerably more prevalent in men than in women, the ratio being about two to one. The great majority of the lesions were basal cell.

Surgery is of value in certain cases with special indications. Curie therapy may be used but no eye-shield will adequately protect the eye in this type of irradiation. Roentgen therapy is the treatment of choice. The author uses 110 kv. (peak) in most cases and a filtration of 0.25 mm. copper. In extensive recurrences he uses 220 kv. (peak) with 1.0 mm. of copper. Eye-shields are used as a rule. Ordinarily 150 r per day is given at the start, this later being raised to 200 and 250 r. The total dose to a lesion 1.5 to 2 cm. in diameter is 4,000 to 5,000 r when given over three to four weeks. In no case should less than 3,000 r be given. Adequate treatment is essential to prevent recurrence which may require drastic treatment resulting in loss of the eye. The author discusses the care of the radiodermatitis which always follows the treatment.

Of the total number of 168 cases of carcinoma of the skin of the orbit reported, 2 cases were not treated, 4 were lost to view, 25 died of intercurrent diseases, 5 are known to be living with carcinoma, 132 have remained well at three years or more, making a 78 per cent survival after three years.

After roentgen therapy of 117 consecutive cases of basal-cell carcinoma not previously treated the author had nine recurrences, all of which were controlled. There was an 86 per cent absolute three year and a 77 per cent absolute five year survival. None of the patients died as a result of the carcinoma. No case of cataract developed in this series of 117 cases.—*J. Paul Bennett, M.D.*

LAUGE-HANSEN, N., and LYNDRUP, SVEND. Hidrosadenitis axillaris and its roentgen treatment (optimum total dose and intenseness). *Acta radiol.*, Feb. 1949, *31*, 129–144.

Hidrosadenitis axillaris with the synonyms staphylodermia sudipara and abscessus glandularum sudoriparum was first described by Velpeau in 1839 as superficial abscesses involving the axillary, mammary and perianal regions. In 1854, Verneuil reported on the basis of purely clinical observations that hidrosadenitis was associated with the sweat glands. Lane was the first to describe this entity in the American literature in 1933.

Summary. The author's investigations show that treatment of this condition must be prolonged over weeks and even months if conservative surgical or insufficient radiological treatment is given.

An analysis of 357 cases of hidrosadenitis axillaris shows that the optimum total dose of roentgen therapy is 1,000–1,200 r given at a rate of 200 r daily. By this method it is possible to cure all cases in an average time of two weeks. Supplementary treatment with surgical incision does not seem to shorten the duration—in fact, the opposite effect is produced. Puncture of abscess formations gives immediate relief of tension and pain.—*Mary Frances Vastine, M.D.*

DALAND, ERNEST M. Radiation necrosis of the jaw. *Radiology*, Feb., 1949. *52*, 205–215.

Any radiologist who treats cancer about the mouth and face is certain to see an occasional case of necrosis of the jaw. Devitalized teeth lead to sepsis. Sepsis creates havoc in irradiated tissues. When roentgen therapy is to be directed to lesions of the mouth, any teeth through which the beam will pass should be removed before treatment is started. Treatment is deferred for one week after the extraction. Antibiotic therapy and thorough mouth irrigations are carried out during this time. Teeth exposed to irradiation should not be extracted for a period of several years. The author has had this impressed upon him time and again. There are no exceptions. Careful mouth hygiene should follow irradiation. The first evidence of bone necrosis is pain. Inspection will show a devita-

lized area of mucosa or periosteum. A little later bare bone will appear. It will not act like the usual bone infection from an abscessed tooth, osteomyelitis or compound fracture. It will not form a spontaneous sequestrum. It will never become with periosteum or mucosa. If the exposed bone is treated by electrocoagulation it will die and separate as a heat sequestrum. There is some chance that the deeper bone will become covered.

Whenever necrosis of the bone appears the surgeon should take over. It will be his province to carry on reconstruction after the radiologist has destroyed the cancer. Surgical reconstruction in these cases is long and tedious. The best method is by a tube pedicle graft constructed from the chest wall.

Several case histories are presented which substantiate the role of devitalized teeth in the production of necrosis of the jaw following irradiation about the mouth and face.—*J. E. Miller, M.D.*

Leddy, Eugene T., and Maytum, Charles K. Roentgen treatment of bronchial asthma. *Radiology*, Feb., 1949, *52*, 199–204.

According to the authors, statistical studies of the results of roentgen therapy of asthma are of questionable value because of multiple etiologic factors. Roentgen therapy is used after specific or nonspecific therapy has failed to produce relief. Mild cases are not treated. The severe and moderately severe cases which are treated constitute about 6 per cent of asthmatics treated at the Mayo Clinic.

The spleen, suprarenal glands, liver, pituitary gland and other areas have been treated with comparable results. Some writers have "treated" patients without the roentgen tube being in operation and have obtained benefit. The authors quote at length from their two previous reports on this subject and give their results. Two techniques have been used by the authors termed "high dosage" and "low dosage." The former consists of large anterior and posterior mediastinal fields. A dose of 500 r, measured in air, is given to each field. The latter technique consists of a 16 cm. square field centered over the sternum and a corresponding posterior field. Each field receives 256 r, measured in air. Intermediate voltage (130 to 135 kv.) is used for both techniques. The authors prefer the low dosage technique and obtain considerably better results with it. They recommend a large series of cases with even lower dosage, suggesting 100 r or even less. With low dosage technique, less than 10 per cent of the cases treated were considered to be failures. Over 60 per cent obtained good results or complete relief.

No criterion for judging which patients will obtain relief is given. The more severe cases apparently have a better chance to obtain relief. Several theories are offered as to why irradiation might benefit asthma, but no proof is offered to support any of their theories.

Several papers are abstracted in this article giving the techniques and results obtained by the authors quoted. These other authors apparently obtained good results in a high percentage of cases also. Treatment is not repeated as long as the relief lasts. The authors consider that their technique offers no danger to the patient even if repeated as many as ten to twelve times over a period of several years.

The experience in the treatment of asthma with roentgen rays has been similar to the experience in treatment of inflammatory or infectious lesions. Lower doses, therefore, may be worth trying.—*J. E. Miller, M.D.*

Read, J. Marion. Graves' disease. *Radiology*, April, 1949, *52*, 557–563.

The author reports the present status of 14 persons who received roentgen therapy of the thyroid twenty-five years ago in the treatment of Graves' disease; toxic nodular adenoma was not included in this designation, which entity the author believes should be treated surgically. The cases were unselected as to severity but had received only non-surgical treatment in conjunction with the irradiation. The initial basal metabolic rates in the series ranged from 23 to 112, the average being 53.4 per cent. Nine of the cases are now living, and well, at ages ranging from thirty-four to seventy-three years. One had a thyroidectomy with only fair results; while one, seventy-one years of age, has chronic heart disease with hyperventilation. Three of the series are dead from causes other than Graves' disease. Five have exceeded the normal life expectancy. The author concludes that the long-term results of roentgen irradiation in Graves' disease yields results which are as satisfactory as those of surgery. This will probably also be true of irradiation with the radioactive isotopes of iodine.—*J. Paul Bennett, M.D.*

Shullenberger, C. C., Watkins, Charles H., and Kierland, Robert R. Experiences with nitrogen mustard therapy. *J.A.M.A.*, March 19, 1949, *139*, 773–777.

The authors report the results of nitrogen mustard therapy in 18 cases of advanced Hodgkin's disease. All of these patients had repeated courses of roentgen irradiation prior to mustard therapy. Most of these patients had noted less pronounced response with each succeeding series of irradiation. Fourteen of these patients died of progression of disease or progressive deterioration of their physical condition. In 4 patients there was little clinical change at the end of the observation period. In some patients there was a measurable regression of involved lymph nodes and spleen after nitrogen mustard therapy. Only 1 of 7 cases with pulmonary lesions showed response, but after fifteen weeks these lesions progressed and failed to respond again. No regression of skeletal lesions was noted. One of 2 patients with liver involvement showed temporary regression but showed no effect after subsequent treatment.

Nitrogen mustard alone or in combination with roentgen rays did not produce any improvement in the anemia or leukopenia in these cases.

Ten cases of lymphosarcoma were treated with nitrogen mustard. In 6 of these, patient's death occurred from the progression of disease. In 1 patient there was complete remission for 2.5 months. Improvement was noted within one week. The patient did not return for additional therapy. Another patient showed a clinical response for 4.5 months. A third patient showed partial remission for six months, and the fourth case showed a partial remission for one mouth.

When lesions of *Mycosis fungoides* responded favorably to nitrogen mustard, the effect was thought to be identical with that of roentgen rays. Resistance to roentgen therapy seems to be an indication for mustard, since the sensitivity of lesions to roentgen rays may return in a few weeks or several months.

One case of lymphoblastoma which failed to respond to roentgen therapy showed a good primary response to mustard. Two patients with leukemic reticulo-endotheliosis showed no favorable response. Seven patients with malignant neoplasms of various types responded poorly or not at all to mustard.

The authors emphasize that nitrogen mustard is a potentially dangerous drug and is capable of severely damaging the hemopoietic tissues when used in the presently accepted therapeutic doses. It is suggested that more cases of lymphosarcoma be treated with mustard alone to properly evaluate the results of this method of treatment.—*Henry L. Jaffe, M.D.*

Bouslog, John S. Roentgen irradiation of thrombophlebitis. *Radiology*, Feb., 1949, *52*, 216–219.

The author advocates the use of radiation therapy in treatment of thrombophlebitis, and feels that it should be added to the many other methods now utilized because:

1. It shortens the duration of the illness.
2. It relieves the symptoms rapidly.
3. It offers a means of treating deep veins when surgery is not practical.
4. It can be easily utilized in acute, subacute and chronic cases.

He reports 2 cases of acute thrombophlebitis in which relief of symptoms was noticed within twenty-four hours, and swelling began to subside within forty-eight hours. Three cases of chronic thrombophlebitis with good results are also reported.

He has utilized 200 kv., 50 cm. target skin distance, 0.5 mm. copper and 1 mm. aluminum filter, and 150 r (measured in air) per treatment area. He feels, however, that the first treatment should be reduced to 50 or 75 r in severe inflammatory cases.

The author feels that most of the cases of thrombophlebitis start in the calf of the leg, and, in such cases, best results are obtained from irradiating both the calf and the iliofemoral region.—*J. E. Miller, M.D.*

Payson, Benjamin, A., and Rosh, Rieva. Carcinoma and other neoplasms of the male breast. *Radiology*, Feb., 1949, *52*, 220–229.

Among the factors contributing to the disappointing end-results in carcinoma of the male breast are the rarity of the lesion and its consequent underestimation by layman and physician so that diagnosis is made too late for successful treatment.

The male's mammary gland remains in a rudimentary state comparable to that in preadolescent females.

From July, 1924–July, 1946, 25 of 1,141 malignant tumors of the breast at Bellevue Hospital's Radiation Therapy Clinic were in

males (27 *benign* tumors of the male breast were seen from 1936–1946). The incidence in the male is estimated variously from 1–2.5 per cent of all breast cancers. Preceding trauma to the breast may well have etiologic significance; the authors' series seems less suggestive regarding the importance of hormonal influences and of previously existing benign mammary tumors.

This carcinoma appears later in life than in females, and the duration of symptoms before seeking medical advice is longer than in females. Because of the relatively small amount of fatty and glandular tissue, skin attachment, nipple retraction, ulceration, and pectoral invasion appear earlier than in the female. Nipple retraction and skin attachment may occur with any tumor (and even infection) in the male breast, hence these are not valid as evidence of malignancy.

In this series, 24 per cent had involvement of the breast alone; 52 per cent of the breast and axillary nodes; 20 per cent of the breast, axillary nodes, and distant metastases. The microscopic appearance is practically the same as in females.

All discrete lesions in the male breast should be biopsied for early diagnosis and radical surgery is the preferred treatment. Postoperative irradiation is recommended. Castration has benefited cases with osseous metastases. Though five-year survival rates vary widely, the prognosis is poor, certainly less favorable than in females.—*Henry G. Moehring, M.D.*

TREVES, NORMAN. Castration as a therapeutic measure in cancer of the male breast. *Cancer*, March, 1949, *2*, 191–222.

The number of reported cases of mammary cancer in the male treated by castration is very small. Only primary inoperable, recurrent, or rarely primary operable cases have been available for such treatment.

The author details the results of 13 cases of male mammary carcinoma treated by orchiectomy, 6 of which were reported by him and others in 1944.

The clinical improvement noted closely parallels similar observations in prostatic cancer treated by castration and includes relief of pain as well as notable healing of the breast tumor, even in those with ulceration. Bone metastases showed varying degrees of regression and healing; soft tissue metastases such as axillary nodes or pulmonary spread were less noticeably influenced.

The biochemical changes produced by testosterone or alpha-estradiol were not seen in castrated patients, indicating that a similar mechanism is not at work in producing the clinical improvement.

Reactivation of the disease after regression due to castration is not influenced by any known measure. Stilbestrol and pituitary irradiation failed to effect any control of the unfavorable progression of recurrence in a small number of cases.

Of the 13 cases reported, 3 were treated by orchiectomy alone; the remaining received other treatment in addition to castration. Two of the 3 cases treated by orchiectomy alone were alive and well four years and three months and three and one-half years respectively after castration. Of the remaining 10 cases, five were alive at the time of the report, with survival times of seven months to five years and five months after castration.

In view of similar, if not somewhat better, results with castration alone than with radical mastectomy (especially in older men), the author proposes the former measure. However, he pleads for results of a larger number of cases than has heretofore been reported.

An expression of hope is also held for the development of indications for the trial of other clinical measures to control breast cancer in men by the present study of ketosteroid patterns on the urine before and after castration.—*W. C. Gallo, M.D.*

KAAE, SIGVARD. Testosterone propionate in the treatment of breast cancer. *Acta radiol.*, Feb., 1949, *31*, 97–112.

In his conclusion the author states that there is no doubt that in many cases of breast cancer, testosterone propionate brings about marked relief of pain associated with improvement in the general physical condition. Sometimes, however, and especially in cases where there is initial hypercalcemia, the therapy may give rise to toxic manifestations. Thus the patient should be observed carefully, particularly after the first injection, in order to ascertain whether or not the serum calcium is controlled. In women who are in the menstrual age, just as good effects can be obtained by roentgen irradiation of the ovaries.—*Mary Frances Vastine, M.D.*

Habibi, M. Deux cas de cancer du sein chez deux fillettes, l'une de 7 et l'autre de 9 ans. (Two cases of cancer of the breast in two young girls, one seven and the other nine years old.) *Bul. Assoc. franç. l'étude cancer*, 1947, *34*, 75–77.

The author presents 2 cases, and his observations as follows:

1. In the medical literature, there are a few exceptional cases of cancer of the breast in young girls of fifteen to twenty years of age. Cancer of the breast of children of seven or nine years is rarely seen. The author describes 2 such cases and feels that probably one of his cases began developing the cancer at the age of six or even at the age of five. In this case when the patient was first seen the tumor had already been present at least two years.

2. In both cases the histopathologic pictures resembled each other and their growth was very rapid. Four figures illustrate the article.—*Panagiotis S. Nemfakos, M.D.*

Gricouroff, G. Du pronostic histologique dans le cancer du sein. (Histopathologic prognosis of cancer of the breast.) *Bull. Assoc. franç l'étude cancer*, 1948, *35*, 275–290.

The author presents his observations and opinions upon the above classifications as follows:

1. Prognostic value of the proposed classification. The occurrence of different growth characteristics that are reviewed show that the degree of malignancy of tumors vary from first towards fourth degree.

We can, according to the hypothesis of this work, use a histopathologic classification for a clinical prognosis, as soon as the number of the cases is large enough to compile statistics.

2. Histopathologic degree and anatomoclinical stage of extension. The two classifications do not superimpose, but are in agreement. The whole histopathologic study agrees with the classification according to the clinical stages. We can conclude that the division into four degrees from a histoprognostic standpoint brings us supplementary information of the malignancy of the tumors and gives us the opportunity to make a certain discrimination between the tumors of the same clinical stage. The author feels that the size of the glandular enlargement is not of great importance since the prognosis of a cancer depends upon the degree of malignancy. The result can be more favorable for a large tumor of first degree than for a small tumor of fourth degree. Statistics on five year cures are as follows:

1st degree tumors—4 patients—3 cures.
2nd degree tumors—2 patients—1 cure.
3rd degree tumors—3 patients—1 cure.
4th degree tumors—7 patients—1 cure.

3. Roentgen therapy pre- and postoperatively. The eventual gain offered to the surgeon by roentgen therapy pre- and postoperatively could not be studied sufficiently to draw valuable conclusions. Since irradiation is applied mainly to the cases which are clinically advanced ones, a comparison of the results of surgery and roentgen and surgically treated ones prove nothing. It is certain that irradiation can have a considerable effect on the tumor. Because there is a large variation in the degree of malignancy of cells in a piece of the cancerous tissue, it is indispensable to make microscopic examinations of fragments extending through all the tumor.—*Panagiotis S. Nemfakos, M. D.*

Gordon-Taylor, G., McWhirter, R., and Cade, S. Treatment of cancer of the breast. *Proc. Roy. Soc. Med.*, Feb., 1948, *41*, 118–132.

The problem of mammary malignancy is probed and an attempt is made to assess the therapeutic value of surgery and radiotherapy.

Gordon-Taylor states that radical surgery alone is the treatment of choice for Grades 1 and 2 of mammary cancer. Irradiation is reserved for patients with inoperable carcinoma, or who are otherwise inoperable.

In a series of 388 patients treated by radical mastectomy a 43 per cent ten year survival rate is reported.

McWhirter reports a series of 2,510 previously untreated breast cancers. Three methods of treatment are reported. They are: (1) radical mastectomy, (2) radical mastectomy and postoperative irradiation, (3) simple mastectomy and postoperative irradiation. The five year survival rates of operable cases treated by the above methods were 36, 44 and 56 per cent respectively. The number of five year cures obtained by simple mastectomy followed by postoperative irradiation was very favorably compared with the survival rates of other groups reporting large series. Recurrence and survival rates are reported in full detail.

Cade states that Stage I and II breast carcinomas are best treated by radical mastectomy. Stages III and IV are suitable only for

palliative measures by radiation and endocrine therapy. Irradiation is useful only in operable breast cancer when used pre- or postoperatively in Stage II cases.

Handley reports a series of breast cancers in which the second intercostal node was excised. If the intercostal node and axillae were free of cancer radical mastectomy was performed. If the second intercostal node was involved a simple mastectomy was performed followed by postoperative irradiation. No survival statistics are given.

Allchin states that preoperative irradiation of radiosensitive tumors resulted in a complete absence of active cancer cells after removal of the breast. Less sensitive tumors showed many "attenuated cells." Preoperative irradiation of Stage II breast cancers gave particularly favorable results.—*D. R. Bernhardt, M.D.*

LOWENHAUPT, ELIZABETH, and STEINBACH, HOWARD L. Clinical response of metastatic lesions of carcinoma of the female breast to hormonal therapy as related to histologic grade of malignancy. *Surg., Gynec. & Obst.*, March, 1949, *88*, 291–294.

Hormonal therapy is a recognized method of control of remote lesions in carcinoma of the female breast. The clinical response is not uniform and various factors have been cited as influencing the prognosticated response. Thus Nathanson states, in regard to stilbestrol, that favorable responses are confined to older women and that in younger women the disease is unaltered or perhaps accelerated. Halberstaedter and Hochman report that typical adenocarcinomas are more susceptible to treatment with estrogens than are anaplastic tumors. Their conclusion, however, is based on pathologic reports with no uniform terminology and no attempt at detailed grading. For these reasons it seems of interest to correlate histologic evidence of growth rate (and by inference physiologic maturity) with the observed response to physiologic modes of treatment.

Summary. Response of remote metastases of carcinoma of the female breast to hormonal therapy is correlated with the histologic grade of malignancy, tumors of low grade responding most favorably. Degree of malignancy cannot be predicted on the basis of age. It is suggested that information obtained by biopsy examination be used as an additional factor in determining the clinical management of each patient.—*Mary Frances Vastine, M.D.*

ERNST, EDWIN C. Probable trends in the irradiation treatment of carcinoma of the cervix uteri with the improved expanding type of radium applicator. *Radiology*, Jan., 1949, *52*, 46–62.

The author reviews past efforts to improve the distribution of radium sources in treatment of carcinoma of the cervix, such as the double cross-arm radium applicator in combination with the semi-fixed lateral colpostats, and the use of additional auxiliary colpostats. He points out the difficulty encountered in packing these auxiliary colpostats in their proper position near the parametrium, and that even when properly placed there was little assurance that they would remain fixed there. He describes his development of a single radium unit type of applicator to replace the multiple separate radiation sources previously packed throughout the vaginal vault. This applicator employs nine equally spaced radium sources, and by having them all in a single applicator relative fixation of the sources is maintained. The applicator is an expanding type so that it may be introduced easily in a contracted form, and the lateral arms expanded to the proper position. This expansion feature allows ease and rapidity of introduction and removal. The actual introduction of the applicator requires less than ten seconds. One or both of the lateral colpostats may be removed. They are needed when there is parametrial extension of the primary cervical os lesion, in order to obtain more effective irradiation of this area. Illustrative drawings and radiation distribution charts are presented. The author points out that the maintenance of uniform distribution of the radium intensities minimizes the development of localized "hot spots," and that therein lies the possibility of further increases in dosage while avoiding local over-irradiation.

The author's paper was one of several on radiation therapy of carcinoma of the cervix uteri presented at the 33rd Annual Meeting of the Radiological Society of North America. Following it is an interesting combined discussion of the several papers.—*D. S. Kellogg, M.D.*

WATERMAN, GEORGE W., and REID, WILLIAM A. Place of deep external x-ray irradiation in the treatment of carcinoma of the cervix by long element needles. *Radiology*, Jan., 1949, *52*, 34–40.

This is a review of the authors' experience at

the Rhode Island Hospital over a ten year period (1933–1942). They present a comparison of five year survival rates in patients treated primarily with radium needles alone with those treated primarily with radium needles plus roentgen rays. They report an "absolute survival rate" of 38.8 per cent, and a relative survival rate of 40 per cent. For the entire group of needle treated cases, the five year survival rate was 44.4 per cent. Statistical tables are presented.

In Stage I and II cases the survival rate with needles alone was reported as 80.4 per cent, while the rate with needles plus external irradiation was 64.9 per cent. In Stage III and IV cases the rate with radium needles plus roentgen rays was more favorable (29.3 per cent). With needles alone the rate in these stages was 22.8 per cent. The authors analyze the factors contributing to these results, as well as the differences in complication rates. They conclude that in the Stage I and II cases there is danger of over-irradiating over the central portion of the pelvis when both the needles and roentgen rays are used. They use a 4 cm. lead strip over the lower abdomen above the symphysis to reduce the overdosage to the paracervical area.

The authors refer to the high incidence of complications in the early stage groups treated by other workers, and contend that it is primarily due to over-dosage. They point out that weaker element sources should be used for a longer time, that treatment should be individualized according to the size and method of extension of the lesion, that the external roentgen irradiation should not be given until eight to twelve weeks after the interstitial irradiation, and that the paracervical area should be protected by a lead shield during external irradiation. The more favorable results in late stage cases, with heavier dosage, is explained on the basis of greater protection of normal tissues by the larger bulk of the tumor.—*D. S. Kellogg, M.D.*

Bowing, Harry H. Immediate and late results of intracavitary and radium therapy for malignant lesions of the cervix. *Radiology*, Jan., 1949, *52*, 1–13.

The author reviews the five year survival experience of the Mayo Clinic with intracavitary radium therapy of cervical cancer. This is a study of the results of various types of radium treatment given 3,798 patients during the period 1915 through 1939. The five year follow-up extends through 1944.

The value of the intensive broken dose method of intracavitary radium treatment of the cervix is discussed. About 700 milligram- or millicurie-hours is the dosage used for each application in the average case of extensive invasion of the cervix. This method is used both for palliation and for cure. For moderately invasive lesions the unit dosage is reduced to about 500 milligram-hours, and for the lesion confined to the cervix a further reduction in unit dosage is employed. The author points out that the total dose should be determined by the response or gross change observed in the malignant lesion. Dividing the dose also furnishes a recovery period for the normal tissues. The systemic effects are usually mild. The patient with extensive invasion will tolerate two applications a week. In the average case of lesions confined to the cervix, and only moderate invasion, as many as four applications a week may be employed.

A comparison of the five year survival rates with various methods of treatment is made on all cases treated from 1915 through 1939, and is presented in statistical form. The author concludes that the present treatment of choice in Stage III, Stage IV, selected Stage I, and most Stage II malignant lesions of the uterine cervix is well planned radium and roentgen therapy.—*D. S. Kellogg, M.D.*

Twombly, Gray H., and Chamberlin, J. Allen. Intravaginal roentgen therapy in cancer of the cervix uteri. *Radiology*, Jan., 1949, *52*, 14–25.

The authors review the experience at Memorial Hospital (New York) with radiation treatment of the cervix uteri from 1918 to the present. In 1943 it was decided to attempt a comparison of various substitutes for the local application of radium against the cervix in the apparatus known as the "bomb."

Beginning in January, 1943, a series of cases treated with intravaginal roentgen therapy was begun. This consisted of four treatments of 500 r each, total 2,000 r, directly to the cervix; 3,000 r was given in the fornices; 120 kv. with 3 mm. Al was used. External roentgen therapy was given simultaneously and was followed by intracervical application of radium. In 1945 the treatment was stepped up, using 130 kv. and increased filtration in Stage I and II cases, and 250 kv. for Stage III and IV cases. The

dosage was increased to 2,500 r to the cervix direct and 3,750 r to the fornices. Since 1946, treatments have been gradually increased in amount, so that most of the patients are now treated with 250 kv. and receive 4,500 r to each of the three intravaginal ports, and occasionally as much as 5,000 r.

The authors discuss the advantages and disadvantages of intravaginal roentgen therapy. Their method of avoiding heavy irradiation of the bladder and rectum is described, with illustrative drawings. The idea of treating cancer of the cervix by intravaginal roentgen therapy alone is suggested. In this connection they report a case of clinically obvious carcinoma of the cervix which regressed after small dosage, so that when next examined five months later it could be diagnosed only by careful microscopic study. The patient had been treated preoperatively, but left medical control before the operation.

It is pointed out by the authors that their only three year results of intravaginal roentgen therapy so far are those treated with low voltage technique, and with rather minimal dosage. More time will be needed to determine if the three and five year survival rates have been improved. It appears that the three year results with intravaginal roentgen therapy, even with minimal dosage, are as good or slightly better than the results by previous treatment methods in the same clinic. It seems reasonable to believe that increasing the penetration and doubling the dosage may further improve the rate of cure.—*D. S. Kellogg, M.D.*

CAULK, RALPH M. Review of ten years experience with transvaginal roentgen therapy. *Radiology*, Jan., 1949, *52*, 26–33.

This is a review of the author's experience with transvaginal roentgen therapy in carcinoma of the cervix from October, 1936, through December, 1946. The various combinations of treatment, in the 346 cases reported, are discussed. Definite survival data are available in 192 of the 202 cases treated prior to 1943, and are presented in a table according to the various stages classified. Fourteen cases represent carcinoma developing in the cervical stump following supravaginal hysterectomy. Of these 14 patients, 10 (71 per cent) have lived from five to ten years. It is interesting to note that 7 of the 14 patients were treated with transvaginal roentgen therapy only. Of these, 6 (85 per cent) are living and well for five years or longer. An "absolute five-year survival rate" of 35 per cent is reported.

The technique of treatment is discussed. Both medium and short wave therapy are used, but it is pointed out that the survival data presented in this report are based upon transvaginal roentgen therapy delivered at 220 kv. (peak). A single portal of entry is used, with as large a diameter of cone as possible, the aim being to irradiate uniformly the cervix, fornices and pericervical tissues. Daily doses of 800 r are given. The total dose has varied over the years from 5,000 r to 8,000 r. It is noted that with the latter dosage a higher percentage of untoward reactions in the vaginal vault occurred. At present a total dose of 6,400 r is given if intracervical and intrauterine radium is to be added, and 7,200 r if supplementary radium is not used. The majority of these patients have a moderately severe diarrhea, but it is stated that this is easily controlled with administration of tr. opii. Bladder reactions are usually mild. Partial vaginal atresia is reported in 21 per cent of cases, and complete atresia in 5 per cent. The author points out that some degree of cicatricial contraction in the apex of the vaginal vault can scarcely be avoided if these patients are to be treated adequately.—*D. S. Kellogg, M.D.*

BUSCHKE, FRANK, and CANTRIL, SIMEON. Roentgen therapy of benign giant-cell tumors of bone. *Cancer*, March, 1949, *2*, 293–315.

In addition to outlining their treatment of benign giant-cell tumors of bone, the authors present valuable contributions for more accurate recognition of indications and limitations of roentgen therapy for this condition. Various questions are raised and answered concerning the reliability of diagnosis, the differentiation between benign and malignant bone lesions, and the danger of development of malignant change subsequent to therapy.

In most cases, adequate roentgenographic study by an experienced radiologist leads to an accurate diagnosis of benign giant-cell tumor of bone; however, neither roentgenographic nor histopathologic findings alone are sufficient to definitely establish the diagnosis. The authors accept the diagnosis as "sufficiently certain only if the tumor is located in typical sites (epiphyses of long bones or mandible), and if it shows the characteristic radiographic appearance and typical histologic findings in a sufficiently representative portion of the biopsy

material obtained from untreated tumor." The response to irradiation cannot be considered of value as a therapeutic test since it may be many months before bone regeneration is demonstrated roentgenographically and valuable time lost should the tumor be malignant. Other bone lesions may show a therapeutic response similar to that seen in benign giant-cell tumor. A case is described by the author which was originally diagnosed benign giant-cell tumor involving the distal end of the radius. Bone regeneration appeared two months after the administration of 6,000 r given in twenty-seven days. Subsequent examination established a diagnosis of osteitis fibrosa cystica. Complete bone regeneration was present four years after treatment.

A single-course treatment is advocated rather than the more commonly used repeated small dose interval series. The authors attempt to administer in one course of treatment lasting four to eight weeks, a total tumor dose accomplishing permanent sterilization without impairing bone regeneration. Uniformly good results have been obtained with tumor doses approximating 4,000 r. Recurrences were found only in rare instances.

In summary, the following points are considered regarding the therapeutic approach:

1. Wide surgical excision is preferred where this is possible without mutilation and functional or cosmetic impairment. Tumors in ribs or upper end of the fibula lend themselves to this treatment.

2. Roentgen therapy is the method of choice for tumors adjoining joints or those in the mandible or maxilla.

3. Tumors inaccessible to wide surgical excision (in vertebrae) are treated by roentgen therapy.

4. "Atypical giant-cell tumors" or those of questionable malignant character are most safely treated by surgical excision if possible. In these cases, inadequate treatment is to be avoided.

5. Curettage in any case is inferior to roentgen therapy and has been found to produce a recurrence rate of 30 per cent. Curettage should never be repeated but recurrences should be handled by wide excision or single course of roentgen therapy. A combination of curettage and roentgen therapy seems to be responsible for the rather exceptional cases of subsequent malignant development. In a large series of adequately diagnosed benign giant-cell tumor, the authors report no cases of malignant change following an adequate dose, single course of roentgen therapy.—*W. C. Gallo, M.D.*

Pendergrass, Eugene, P., and Kirsh, David. The role of irradiation in the management of carcinoma of the breast. *Radiology*, Dec., 1948, *51*, 767–778.

Four hundred and six cases of breast carcinoma seen at the University of Pennsylvania Hospital from 1932 to 1939 are reported.

One of the authors had previously reported on 387 cases of breast carcinoma seen from 1902 to 1931 and expressed the opinion that postoperative irradiation and surgery were not superior to surgery alone. Since 1936 routine postoperative roentgen therapy has been abandoned and the present series includes five year follow-ups on a number of cases treated by surgery alone.

The Steinthal classification was used for this material. However, in the future the authors plan to use the classification of Portmann which combines both clinical and pathological criteria.

Various terms such as operability, inoperability, radical resection, simple resection, preoperative, postoperative and prophylactic irradiation and their combinations, as well as the irradiation for operable or inoperable carcinoma, or recurrences and metastases, are defined. Irradiation techniques and dosages for the various periods are described.

Of the 406 cases, 350 were subjected to surgery and 56 were treated by irradiation alone. The latter treatment was used if the lesion was considered inoperable, or surgery was refused by the patient, or if there was a medical contraindication. Two hundred and forty-five cases were operated upon at the University Hospital and 145 cases were operated upon elsewhere. Of these 350 surgical cases, 188 received postoperative roentgen irradiation to the operative site and lymph nodes areas, while 162 received no irradiation except when metastatic or recurrent disease developed.

The data have been analyzed statistically and are presented in twelve tables. When possible it was compared with the data of the 387 cases previously reported. The present series showed an increase over the former ones in the five year survival rate from 26 to 42 per cent. An evaluation of the percentages as shown in the tables might suggest that in some cases superior results are attributable to irradiation. How-

ever, when these figures are subjected to statistical analysis, the results were insignificant and could be attributed to two factors: "(1) either there is no improvement in the end results of treatment of carcinoma of the breast which could be due to irradiation, or (2) if there is improvement, it is so slight that with the samples of the size considered here, significant improvement is not evident."

The authors have relegated irradiation to a palliative role for osseous or pulmonary metastasis, or for any other complications which might arise and for which irradiation may be of value.—*Norman Heilbrun, M.D.*

Costolow, William E. Carcinoma of the cervical stump. *Radiology*, Jan., 1949, *52*, 41–45.

This is a review of the experience of the author's clinic with 165 cases of carcinoma of the cervical stump, during the period 1922–1947. These patients constituted 8.0 per cent of the total of 2,071 cases of carcinoma of the cervix during that period. Sixty-three of the 165 cases of stump carcinoma occurred during the first two years after supravaginal hysterectomy. These were considered as probably present at the time of operation, and therefore not true carcinoma of the cervical stump.

The treatment of carcinoma of the cervical stump is discussed. Where possible, radium is inserted into the cervical canal. In many cases radium was packed against the cervical stump and vault. The total dosage varied from 4,000 to 5,000 milligram-hours, or 2,880 to 3,600 gamma roentgens. In addition, external roentgen therapy was given, often immediately following the radium cycle. From 1922 to 1934, 180 to 200 kv. technique was used. Since that time 450 to 500 kv. has been employed. Tissue dosage of 3,000 r to 5,000 r to the mid pelvis was given. Treatment is fractionated over a period of five or six weeks. The author points out that the stump cases usually present more difficulty and complications due to reaction in the bladder and rectum, and therefore are given less dosage than for primary carcinoma of the cervix. A five year survival rate of 32.5 per cent is reported. The five year survival rate, without evidence of disease, is 30.7 per cent.—*D. S. Kellogg, M.D.*

Mullenix, Ralph B., and Prentiss, Robert J. Critical analysis of treatment of bladder tumors. *Urol. & Cutan. Rev.*, Feb., 1949, *53*, 65–67.

The authors have chosen the 87 cases of bladder carcinoma which they have followed in their private practices for ten years. The cases have been graded both clinically and histopathologically. The criteria for clinical grading is concisely presented. The methods of treatment have been variable. The majority were treated by the transurethral route alone, or in combination with roentgen rays or radon. No cases were treated by irradiation alone.

The results are classified as "good," "fair, or bad." Explanation of these terms is given. The authors believe that the judgment of "cure" of vesical neoplasia cannot be based on an arbitrary span of time and that only cystectomy can assure a cure. Only one patient in their series was treated by cystectomy.

The gross results of all methods of treatment showed 45.5 per cent "Good" results. It is the authors' opinion that transurethral methods, with or without irradiation, offer the best chance to the greatest number of patients. They warn that all patients, except in cystectomy, should undergo cystoscopy at regular intervals.—*William G. Johnson, M.D.*

RADIOISOTOPES

Stanley, M. M., and Astwood, E. B. The response of the thyroid gland in normal human subjects to the administration of thyrotropin, as shown by studies with I^{131}. *Endocrinology*, Jan., 1949, *44*, 49–60.

Twenty-three normal human subjects were given single injections of 15 or 30 milligrams of thyrotropin and studies with I^{131} were made. There was a marked acceleration of iodine uptake by the thyroid which reached a maximum in twenty-four to forty-eight hours. No change was found in the first eight hours. After four or five days, the rate of turnover of iodine returned to preinjection levels. By the use of mercaptoimidazole to prevent organic binding of iodine, it was found that the iodine concentrating capacity of the thyroid was similarly increased by thyrotropin. It was not possible to detect any loss of stored thyroid hormone after a single injection of thyrotropin.—*John W. Karr, M.D.*

Werner, Sidney C., Quimby, Edith H., and Schmidt, Charlotte. Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine (eight-day half-life). *Radiology*, Oct., 1948, *51*, 564–581.

Studies of uptake of radioiodine by the thy-

roid gland in 30 normal cases showed 11 to 34 per cent of an administered tracer dose of 50 to 75 microcuries of radioactive iodine at the end of twenty-four hours. In 28 cases of toxic diffuse goiter uptake was 44 to 76 per cent and in 5 hypothyroid cases 1 to 4 per cent. The percentage urinary excretion of the isotope in normal cases averaged 52, in toxic goiter 22 and in hypothyroids 55. The uptake of the isotope is of value in determining dosage.

The cases used in the therapeutic studies numbered 40, 18 primary toxic goiters without previous treatment and 22 cases recurrent after operation or without remission on cessation of antithyroid medication which had been given for one to two years. No true hyperophthalmic goiter was treated. The remissions were 88 per cent. All cases received between 3 and 4 mc. regardless of toxicity of the goiter or gland size.

The results were directly proportional to the dose per estimated gram of gland (with no failures where the dosage was 150 μc. per gram), to the μc. retained per gram and to the actual administered dose of radiation in terms of equivalent roentgens.

There were 11 failures and 6 successes in 17 cases with basal metabolic rates of 50 per cent or greater, but 23 successes and 6 failures in 29 cases with rates below 50 per cent. It may be that the high metabolic rate cases were associated with larger glands and thus lower dosage per gram.

As yet it is not possible to evaluate effect of gland size per se. Cases showing a higher percentage uptake have a larger number of successes. It will be interesting to see results of the treatment of the larger glands with large doses.

The basal rate returned to normal in most cases at the end of the second or middle of the month. Four cases of transient hypothyroidism occurred three to four months after ingestion and cleared in one month or slightly longer. The doses varied from 2,900 to 8,600 equivalent roentgens. Basal metabolic rate depression and serum cholesterol rise were noted during the hypothyroid period with return to normal on recovery. Sore throat and cough occurred in 6 cases and a tender gland in 2. Three cases of increased toxicity occurred without cardiac failure or thyroid storm and all were failures in their first course. No radiation sickness occurred.

In most cases the gland reduced to normal size in the successful cases. In the failures some reduction occurred but not to normal.

Radiation hazards are discussed in regard to the patient, to the operators and to persons near the radioactive material.

The previous use of stable iodine from iodized salt, gallbladder dye or iodine in preparation for operation decreases radioiodine uptake sharply and may cause a serious error.

The 88 per cent remission rate compares favorably with surgery (90 per cent) and surpasses the results of roentgen therapy and thiouracil and propylthiouracil treatment. The dose which seems satisfactory to produce a remission without permanent underfunction and hypothyroidism is tentatively 125 μc of I^{131} per gram or a radiation dose of about 6,000 e.r. Treatment after the third month of pregnancy should be avoided. Malignant exophthalmos has not followed radioactive iodine. It is necessary to wait at least three months before retreatment.—*J. Maxey Dell, Jr., M.D.*

Rawson, Rulon W., and Skanse, Bengt N. Radioactive iodine, its use as a tool in studying thyroid physiology. *Radiology*, Oct., 1948, *51*, 525–531.

A brief review of major research in the use of radioactive iodine as a tracer in studying the functions of the normal and abnormal thyroid is presented. The authors are engaged in evaluating the effect of radioactive iodine upon these functions. Their studies indicate that certain so-called tracer doses cannot be administered without altering the normal physiology of the gland. They point out that the minimal amount of radioactive iodine which can be administered without altering thyroid function must be determined so that tracer doses can be kept with in this limit, even if the dosage is so small as to require perfection of more sensitive measuring equipment to detect the tracer substance. The same holds true for other radioactive isotopes.—*George Cooper, Jr., M.D.*

Chapman, Earle M., Skanse, Bengt N., and Evans, Robley D. Treatment of hyperthyroidism with radioactive iodine. *Radiology*, Oct., 1948, *51*, 558–563.

Comparative series of 65 patients each are paralyzed, one with I^{130} and one with I^{131}. The average single effective dose by mouth was 32 millicuries of I^{130} and 10 of I^{131}. Fifty-one of the I^{130} and 52 of the I^{131} cases were classified as responding well without relapse. There were 6 cases of radiation sickness with I^{131} and none with I^{130}, 11 cases of hypothyroidism with

I^{130} and 4 with I^{131} and 3 cases better, but toxic six months after treatment with I^{130} and 8 with I^{131}. Although the authors do not definitely state that I^{131} is superior, their data seem to indicate this.

The use of radioactive iodine is advised against after the third month of pregnancy. The danger of producing myxedema in a patient without hyperthyroidism is unlikely due to the high rate of excretion. Toxic effects of I^{130} were nausea, slight fever, and swelling and tenderness of the thyroid for a few days. Toxic effect of I^{131} was an exacerbation of thyrotoxicosis and studies are being carried out with preliminary treatment of severely toxic patients with drugs of the thiouracil series. Histopathologic changes in one case showed edema and separation of the cells from the basement membrane, but no fibrosis.—*J. Maxey Dell, Jr., M.D.*

Frantz, Virginia K., Quimby, Edith H., and Evans, Titus C. Radioactive iodine studies of functional thyroid carcinoma. *Radiology*, Oct., 1948, *51*, 532–552.

This paper, while primarily a preliminary report of the authors' work with I^{131} in thyroid carcinoma, is also a detailed account of their experience with thyroid carcinoma in general. A statistical analysis of cases of thyroid carcinoma from 1924 to 1947 is presented.

Sixty-eight cases of possible carcinoma of the thyroid were studied with tracer doses of I^{131}, 32 of which were proved to be carcinoma.

The undifferentiated Grade 2 and Grade 3 tumors, pure papillary carcinomas, Hürthle cell tumors, benign or malignant, showed no uptake of radioactive iodine. The uptake has been variable in the malignant adenoma group, and the authors feel a larger series is needed before they can affirm the hypothesis that the greater the degree of differentiation, the higher the functional activity. Radiographs of some of these lesions are presented.

The possibility that effective I^{131} therapy of metastases might depend upon the removal of the functional thyroid gland is considered. Total thyroidectomy is recommended, even if the primary focus has been removed, in cases with malignant functional adenomas with metastases to bone, and in cases with multiple foci in the lateral neck with or without involvement of the neck itself. The function of metastatic foci may be enhanced by physiologic demand after thyroidectomy. These metastases may be further stimulated by thyreotropic hormone.

In cases with borne metastases doses of 50 to 100 mc. are given. In cases with only local disease in the neck radically removed at operation, the authors propose to give smaller postoperative prophylactic doses for possible small foci not removed surgically.

A detailed study of the authors' experience with I^{131} in primary and metastatic thyroid carcinoma is presented.—*Gordon J. Culver M.D.*

Marinelli, L. D., Trunnell, J. B., Hill, R. F., and Foote, F. W. Factors involved in the experimental therapy of metastatic thyroid cancer with I^{131}. *Radiology*, Oct., 1948, *51*, 553–557.

The differential localization of radioelements in neoplastic cells in concentrations sufficient for tumor eradication offers an approach to the control of cancer by systemic means. Successes in the treatment of metastatic thyroid cancer with radioactive iodine led the authors to investigate this form of therapy. The presentation is a progress report, detailed reports on related physiology, physical methodology, therapy and pathology being deferred until results warrant their publication.

Over a twelve month period 18 cases of thyroid cancer were investigated to determine suitability for treatment with I^{131}. All had metastases. Nine were chosen for treatment and exhaustive studies, and only 2 showed sufficient retention of I^{131} in the tumor to warrant immediate experimental therapy. One illustrative case report is presented.

Of the cell types, metastatizing struma shows maximum uptake of the isotope. Tumors with orderly cellular structure in follicular arrangement containing colloid-like material show moderate preference for the isotope. Only one high grade malignancy—a solid, alveolar carcinoma—has been reported to retain I^{131}. Papillary and Hürthle cell varieties showed no retention. Thick section radioautographs showed that uniformity of radiation was seldom obtained. For this reason experimental therapy was confined to later stages of the disease when conventional therapy would have little value.

Although accurate dosimetry is not yet possible, several means of arriving at approximate dosage are offered: (a) ascertaining the response of a single lesion to external roentgen therapy or interstitial radiation; (b) determining the tumor dose by estimating tumor volume;

the I^{131} content and its effective half-life by external measurements with suitably calibrated Geiger-Müller counters; (c) calculating the "marrow" dose by assuming it approximately equal to the dose received by the blood. The latter is calculated on a basis of I^{131} concentration as a function of time following the administration of tracer doses.

Therapy with I^{131} is possible only when the cells of the thyroid cancer share with the parent gland pronounced avidity for the isotope. Destruction of normal thyroid tissue with the production of myxedema is the consequence of satisfactory tumor inactivation. Radioactive iodine causes minimal damage to normal structures close to tumor masses due to the short range of the beta radiation emitted, but damage to blood, bone marrow, liver and kidneys in the path of the iodine must be minimized. Physiological means must be sought to enhance the concentration and permanence of the isotope in the tumor, as well as to favor its rapid elimination from vulnerable parts of the body. The influence of thyroidectomy, administration of thyrotropic hormone, antithyroid medication and altered renal function were investigated, but no claim can as yet be made as to their correct therapeutic use. Thyroidectomy has produced some encouraging results. Means ought to be found to decrease the isotope concentration in the sputum, gastric juice and urine without impairing the concentration in tumors. In dosages of 100 millicuries or more, one must be alert to early radiation damage as evidenced by transient moderate lowering of the blood count, impairment of salivation and occasional symptoms of cystitis. Thyrotoxicosis of an acute, severe form is an immediate complication. It is apparently due to the breakdown of thyroid follicle cells and the release of large amounts of thyroglobin. The authors conclude that preliminary results warrant further clinical trial of this type of therapy.—*Gordon J. Culver, M.D.*

MISCELLANEOUS

Taylor, Henry K. An apparatus for automatic multiple exposures. *Radiology*, Jan., 1949, *52*, 107–111.

The author discusses several methods which have been used for rapid serial roentgenography, in angiocardiographic examinations. After a comparison of the various multiple exposure techniques in use at the present time, he concludes that the results from cineroentgenography and cinefluorography, while good, are not as good as those with any of the large-film techniques. He points out that the many exposures with cineroentgenography and fluorography are desirable, but from the standpoint of detail they leave much to be desired.

An apparatus is described which mounts eight 14 by 17 inch films on an octagonal drum. The drum is rotated by a Geneva drive consisting of a rotating arm with two driving rollers attached to it. A description of the entire mechanism is given, together with schematic drawings and the name of the manufacturer. The device measures 2 by 4 by 5 feet and is stationary. The cycle of eight exposures can be automatically made in the minimum period of eleven seconds and a maximum of twenty-two seconds. An electrocardiographic device can be adapted to this apparatus so that exposures can be pre-set for any portion of the cardiac cycle.

Plans for a new improved apparatus are discussed. With the newer model the eight exposures will be made in seven instead of eleven seconds. Other features will add to its usefulness, such as the ability to make the exposures in either erect or horizontal positions, the mounting of Lysholm grids, and the use of adaptors so that smaller cassettes may be used as well as the 14 by 17 inch size. In addition to angiocardiography, this apparatus may be used for aortography, cerebral arteriography, peripheral arteriography, and venography. It may also be used for ventriculography and encephalography.—*D. S. Kellogg, M.D.*

Chapman, Don W., Gugle, Lloyd J., and Wheeler, Paul W. Experimental pulmonary infarction. *Arch. Int. Med.*, Feb., 1949, *83*, 158–163.

Twenty-four dogs were used in an attempt to produce pulmonary infarction. No infarction resulted in 12 normal dogs in which intravascular clots were released. Pulmonary congestion was produced in 4 dogs by the administration of alpha-naphthylthiourea (ANTU), but no gross or microscopic evidence of pulmonary infarction was demonstrable. Of 8 dogs that received the drug prior to the release of emboli, 3 revealed pulmonary infarction distal to the embolism and 4 revealed alveolar hemorrhage distal to the embolism.

Clinical and autopsy observations suggested

that pulmonary congestion or edema, or both, were prerequisites for infarction to follow an embolus to the lung. ANTU was employed, therefore, because it seemed to be the best method to produce pulmonary congestion and edema for the twenty-four to seventy-two hours required for true infarction to occur. This necessitated the use of large doses (2 mg. per kilogram administered intravenously) of ANTU. When smaller doses were employed, only transient pulmonary changes occurred, and with larger doses the dogs uniformly died within twenty hours.

Apparently, obstruction of a pulmonary artery, or one of its branches, by an embolus does not cause infarction distally because blood supplied by the bronchial arteries or through anastomoses between intralobar pulmonary arteries is adequate to maintain nutrition. It appears, therefore, that, if circulation in the bronchial arteries and/or pulmonary intralobar anastomoses are interfered with by pulmonary edema or congestion, alveolar necrosis (infarction) results.—*Eugene J. McDonald, M.D.*

LEBLOND, C. P., and GROSS, J. Thyroglobulin formation in the thyroid follicle visualized by the "coated autograph" technique. *Endocrinology*, Nov., 1948, *43*, 306–324.

The method of study was to examine the thyroid glands of rats and guinea pigs after the administration of radioactive iodine by the use of autograph technique. The authors have shown some fundamental aspects of the thyroid cell—viz., thyroglobulin is formed in the cell and the polarity of secretion is toward the colloid. There is found considerable difference in the activity of follicles in various portions of the gland since those under the capsule and in the isthmus are less active. Excretion of thyroid hormone probably results in the colloid and the diffusion of the resulting fragments through the epithelial wall of the follicle. The methods of study in this work are those used in the general study of radioautography.—*John W. Karr, M.D.*

BOCCHI, ERCOLE. Sulla ricerca di sostanza vagale in corrispondenza della superficie di sezione del nervo irradiato. (Concerning the search for a vagus substance liberated from the sectioned end of an irradiated nerve.) *Radiol. sperimentale*, Nov.-Dec., 1947, *1*, 60–68.

The author reviews the literature quite thoroughly with respect to liberation of a hormone-like substance from a nerve stimulated by various physical agents, and in particular a faradic current. In his experiments the author isolated and sectioned the vagus nerve at the base of the neck in five dogs. With the cut end of the nerve in Ringer's solution, the proximal portion of the nerve was irradiated with 600 to 2,000 r (measured in air) with both soft and penetrating rays. As a result he was unable to demonstrate the liberation of an acetyl-choline substance and concluded that it was not possible to isolate a hormone substance from the sectioned end of an irradiated nerve.—*Lucien M. Pascucci, M.D.*

GOLDFEDER, ANNA. Further studies on the radiosensitivity of tumors autogenous to homozygous hosts. *Radiology*, Feb., 1949, *52*, 230–238.

Two analogous mammary adenocarcinomas (from two different inbred strains of mice) differed widely in radio sensitivity as measured *in vivo* (by prevention of proliferation on reimplantation, after irradiation, into hosts of the strain from which each tumor originated.) The "further studies" were *in vitro* observations of the metabolic activity and growth characteristics in tissue culture of irradiated and non-irradiated portions of the two tumors.

In tissue culture, the tumor which had been *less* radiosensitive in the *in vivo* experiments, proved to be the *more* radiosensitive; this tumor was also the faster growing and showed the greater aerobic glycolytic activity. This reversal of relative radiosensitivity from *in vivo* to *in vitro* experiments may be explained, speculatively, by: (1) the mechanism of a tumor to elicit an adequate vascular supply in the host may be impaired by radiation to a different extent than the growth and survival of the tumor cells themselves; (2) the abnormal differentiation promoted by radiation is not the same in the two tumors; i.e., despite their morphological similarity, the tumors are physiologically quite different.

This type of *in vitro* experiment permits study of intrinsic qualities of a tumor, unobscured by host factors.—*Henry G. Moehring, M.D.*